# GENETICS,
# RADIOBIOLOGY AND RADIOLOGY

# Genetics, Radiobiology And Radiology Proceedings, Mid-Western Conference


*By*

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*Chairman, Committee on Radiology*
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*and*

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# PREFACE

The simultaneous release in June, 1956, of reports by the United States National Academy of Sciences-National Research Council on "The Biological Effects of Atomic Radiation" and the British Medical Research Council on "The Hazards to Man of Nuclear and Allied Radiations" produced an intense interest in the use of ionizing radiations in medicine. These reports not only focused the attention of the public on this subject, but also publicized the genetic hazard that can accrue from small amounts of radiation and intensified the efforts of the medical profession to minimize radiation dosage from the use of x-rays.

In the assessment of possible deleterious effects arising from the medical and dental use of x rays, it must be clearly understood that (1) only small amounts of radiation are used in clinical examinations, and (2) the exposures are limited to local or segmental areas of the body as opposed to total body irradiation. As will be brought out in these proceedings, the deleterious effects of radiation of this order are largely the genetic effects which depend on exposure to the gonadal tissues and which are of long range concern to the human race.

It should be pointed out that the information contained in these two reports was based largely on the work of the National Committee on Radiation Protection and the Committee on Radiological Units and Measurements. Since 1931 these bodies have formulated the standards for the safeguarding of patients, the occupational personnel and the public. Their work provided the foundations for the *Handbooks* on radiation of the National Bureau of Standards. The recommendations of these Committees and those contained in the handbooks have proven to be practical in application and to have provided effective protection. What has not been widely appreciated, is that small amounts of radiation can be a genetic hazard when delivered to the reproductive glands, and that the widespread use of radiation in medicine has expanded

enough to yield a significant average gonadal dose to the population.

The Committee on Radiobiology of the Academy Research Council felt that measures should be instituted to call attention to these problems and that one of the best means would be to set up three regional conferences, one for the eastern states, one for the states in the middle west, and one for the western states. Those invited to the Conference would be the professors of genetics, radiobiology and radiology. In this way a forum would be set up for a free and informal interchange of knowledge in these fields. The geneticists and the radiobiologists could teach the radiologists about the genetic hazards and the radiologists in turn could show what was being done to minimize radiation dosage to the gonads and something of the practical aspects incurred in solving these problems. Participants would in turn disseminate the information through their teaching programs to the residents, interns and medical students attending their classes. The Midwestern Conference, held on May 2, 1958, was eminently successful in that there were four professors of genetics, four professors of radiobiology, and twenty-one professors of radiology who participated.

Considerable interest was expressed in the possible somatic effects following radiation exposure of the body tissues and these were thoroughly discussed during the Conference. It was evident that the possibility of shortening the life span from the small amounts of radiation delivered during diagnostic examinations is extremely remote. Likewise, the possibility of inducing leukemia by radiation from diagnostic examinations is also very remote. However, it is a less remote possibility in the radiographic examination of pregnant women who require special care when undergoing these procedures.

The use of ionizing radiation in the treatment of benign conditions requires re-evaluation in the light of deleterious effects of both the genetic and somatic types. This is especially true in radiation of a persistent thymus gland and in the irradiation of the ovaries in infertility, both of which are procedures that have already been largely abandoned and should be done away with completely. Similarly, heavy irradiation of the entire spine for degenerative

arthritis is also open to question, although these cases must be carefully evaluated on an individual basis. The development of the sulfa drugs and the antibiotics have made it possible to do away with the superficial radiation treatment of many benign skin conditions Here the dermatologists have had to re-evaluate many conditions that they formerly treated by radiation. These and similar problems were brought up for discussion at the Conference and it was surprising to see the uniformity of opinion that existed in the management of these conditions.

In discussing the deleterious effects of radiation, one must not lose sight of the tremendous benefits that have accrued from diagnostic radiology in the practice of medicine, nor of the great contributions it has brought and is still bringing to the health and well-being of mankind. The rapid and widespread use of diagnos-

[illegible]

of uncertainty from medical diagnosis It is indispensable. In any situation, we must always weigh the benefit to be gained against the possible hazard. This decision must always remain with the attending physician for it is he who must decide what is best for the patient. The health and welfare of future generations must depend on the health and welfare of the generation before us.

An indirect benefit of the Conference will be the dissemination of accurate information on these problems to the public, many individuals of which have developed an almost psychiatrical fear of radiation. They do not know what they fear. They are just afraid. The time has come when we must help them realize that this is the nuclear age and that they must learn that they can live in it safely, both physically and emotionally. Our goal is to keep all forms of controllable ionizing radiation to a minimum so that we may enjoy the benefits and the developments afforded by the harnessing of nuclear energy. This applies to ionizing radiation for medical use as well as for other purposes. As a guide, we might keep in mind that no matter what the gonadal dose is from diagnostic examinations, it is too high if it can be reduced. By the same token, let us realize that the gonadal dose from a radiographic examination of the chest is comparable to about one-fourth the

amount of natural radiation that one receives on an airplane flight from St. Louis to Denver. In the discussion of these problems, let us always try to keep them in the proper perspective.

WENDELL G. SCOTT, M.D.,
*Editor*

## ACKNOWLEDGMENTS

In the publication of the proceedings of the Conference, I am much indebted to my associate, Dr. Bernard Loitman, who ably assisted me in the proofreading, and to my secretary, Miss Barbara Sampley, for her splendid transcribing of the recordings of the Conference and efficient handling of the correspondence.

We thank our publisher, Mr. Charles C Thomas and staff, for getting the material promptly published and for their willingness to accept the contractual provisions suggested by the National Academy of Sciences

To Dr Titus Evans and Dr. Hymer Friedell I am indebted for their suggestions in developing the program.

Above all, I want to thank those geneticists, radiobiologists, and radiologists who made the formal presentations at the Conference and who subsequently were obliged to check their transcription. It was their work that made this volume possible.

It has been a pleasure to plan the Conference and to arrange for the proceedings, for throughout we have received the full support and cooperation of the officers of the National Academy of Sciences-National Research Council as well as their Committees on Radiobiology and Genetics

WENDELL G. SCOTT, M.D.

# INTRODUCTION AND PLAN OF CONFERENCE

WENDELL G SCOTT, M.D., Chairman

*Dr. Scott:* It is a pleasure to welcome you on behalf of the National Academy of Sciences-National Research Council and its Committee on the Biological Effects of Atomic Radiation. This Conference is one of three authorized by the Academy-Research Council under the guidance of Dr. Hymer Friedell of the Committee on Radiobiology. These conferences are designed to develop a better understanding of the genetic problems arising from the medical use of ionizing radiation among the geneticists, radiobiologists, and radiologists. They are to be informal forums for the exchange of ideas and knowledge between these groups about possible radiation hazards and their control in the practice of medicine.

The program for the Conference is divided into two sections. The morning will be taken up with a discussion of the fundamentals of radiobiology and genetics. This is designed primarily for the edification of the radiologists They are deeply interested in the newer concepts of the effects of radiation on biologic processes in general and in particular the effects on the genetic mechanism They are interested in the practical applications of them in the medical use of ionizing radiation and will want to discuss them and to ask questions This is to be an informal conference for an exchange of knowledge that can be of mutual help

The afternoon session will be devoted to the clinical problems of how to minimize the radiation genetic effects in the daily work of the radiologist The program will be opened by Dr. Titus Evans, Head, Radiation Research Laboratory, College of Medicine, State University of Iowa He is a member of the Committee on Radiology of the Academy-Research Council and will serve as Moderator for the morning session

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*Moderator:* Titus Evans, Ph D.

AFTERNOON SESSION

*Moderator:* WENDELL G. SCOTT, M.D

# GENETICS,
# RADIOBIOLOGY AND RADIOLOGY

## MORNING SESSION

## FUNDAMENTALS OF RADIATION GENETICS

*Moderator: Titus Evans, Ph.D.*

# SITE AND MECHANISM OF RADIATION ACTION (CELLULAR, HISTOLOGIC AND SYSTEMIC)

By

TITUS EVANS, Ph D.
*Head Radiation Research Laboratory*
*College of Medicine*
*State University of Iowa*
*Iowa City, Iowa*

I am between the pure scientist on the one hand and the clinician on the other. My talk will be introductory, directed to the geneticists to show them that the radiologists know something about radiation effects, and to the radiologists so that they can see the background for what the geneticists have in mind. I would like to remind the geneticists and radiobiologists that our radiologists are busy clinical physicians. They are worried about patients, budgets, personnel, gastro-intestinal examinations, etc. We have taken them away from this environment for a little bit. We will lead them into the scientific discussions slowly and if something is not clear, we wish to have them ask questions.

I will review briefly some of the basic principles of radiobiology The radiologists have the responsibility to explain to people who come to them and say, for example, "I've had trouble hiring technicians They're scared to death of radiation." What must he tell them? A few days ago on the bus, I heard a man say, "Gee, I read in the paper this morning that the sun is going to irradiate us all to death" With so many lay people being concerned about radiation, we have to be able to explain its effects in general terms Three or four years ago, I attempted to meet this problem by making some simplified charts.

If someone says, "I'm afraid to work with radiation," you can point out to him that he lives in a radiation environment. We have radio active materials in our bodies So, it isn't a question of

avoiding radiation. It's a question of avoiding excess amounts or more than acceptable levels (Fig. 1).

The second slide takes up the question of amount of body exposed to radiation (Fig 2). Even today, some people in adding up the exposures to a person will include the exposure from a dental x-ray, covering one square inch of the body, to whole body exposures and try to come up with a figure for the total accumulative exposure. In one sense, this is entirely wrong inasmuch as exposure to the whole body is more serious than exposure to various parts alone As long as an organ is protected with lead, it will not suffer a direct effect from the radiation. On the other hand, we have to realize that something more is involved than the volume dose We must try to avoid, as much as possible, excessive whole body irradiation because it affects all of the bone marrow and other regenerative organs

(Fig 3) The severity of radiation damage is related to the intensity of the exposure In the investigations of McComb and

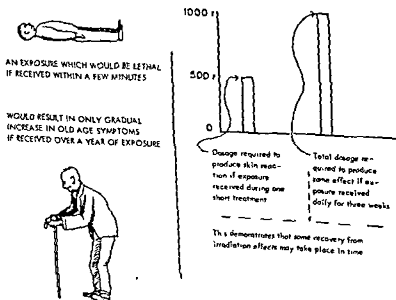



Fig 4—Severity of damage is related to the intensity of the exposure

Figure 3

| | | |
|---|---|---|
| 1000.0 r | >Exposure of small areas for treatment | BIOLOGICALLY EFFECTIVE EVEN IN SINGLE EXPOSURES |
| 100.0 r | | |
| | >Exposure of parts of body during fluoroscopy and photofluoroscopy | |
| 10.0 r | | NOT HARMFUL IN SINGLE OR INFREQUENT EXPOSURES |
| 1.0 r | | |
| | >Exposure of parts of body during chest X-ray, etc. | |
| 0.1 r | | ACCEPTABLE DAILY *EXPOSURE* |
| | >Possible exposure of *X-ray and radium* workers | |
| 0.01 r | | |
| 0.001 r | >*Radium in body* | NATURAL LEVELS OF DAILY EXPOSURE |
| | >$K^{10}$ and $C^{14}$ in body | |
| 0.0001 r | >Cosmic radiation | |

Figure 1

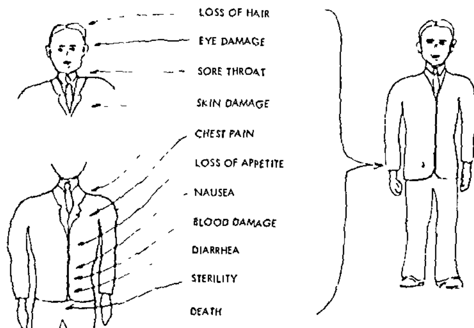



*Fig. 2—Severity of damage is related to the region and amount of the body exposed*

Figure 2

avoiding radiation. It's a question of avoiding excess amounts or more than acceptable levels (Fig. 1).

The second slide takes up the question of amount of body exposed to radiation (Fig. 2). Even today, some people in adding up the exposures to a person will include the exposure from a dental x-ray, covering one square inch of the body, to whole body exposures and try to come up with a figure for the total accumulative exposure In one sense, this is entirely wrong inasmuch as exposure to the whole body is more serious than exposure to various parts alone As long as an organ is protected with lead, it will not suffer a direct effect from the radiation. On the other hand, we have to realize that something more is involved than the volume dose We must try to avoid, as much as possible, excessive whole body irradiation because it affects all of the bone marrow and other regenerative organs

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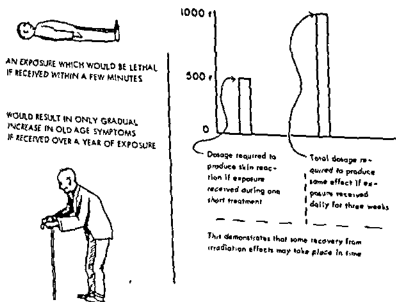



Fig 4—Severity of damage is related to the intensity of the exposure

Figure 3

Quimby on skin erythema, they found that by fractionating the dose, they could prolong the latent period for the appearance of radiation effects and that more radiation could be given in these fractionated exposures to produce the same effect. It is known from animal experimentation that the effect of dividing the exposure into a number of small ones greatly decreases the acute and also the sub-acute reactions. It may not decrease the delayed effects so much, but it certainly does reduce the more acute reactions.

THE MOST SENSITIVE CELLS ARE LYMPHOCYTES OF THE BLOOD AND OTHER CELLS WHICH ARE SIMPLE IN STRUCTURE AND HAVE A SHORT NATURAL LIFE SPAN










INTERMEDIATE IN RADIO-SENSITIVITY ARE CELLS WHICH ARE NOT USUALLY WORN OUT SO RAPIDLY AND ARE MORE STRUCTURALLY COMPLEX










MORE STRUCTURALLY DIFFERENTIATED AND LONG LIVED CELLS APPEAR TO BE RESISTANT BUT WHEN DAMAGED ARE NOT EASILY REPLACED

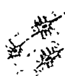






Figure 1

(Fig. 4) This slide demonstrates the response in the different tissues If we are interested in early reactions, we will see these in tissues that are rapidly growing, such as the epithelial cells and the blood cells. Those intermediate in response are the ones that are intermediate in reactivity to things in general, the ones whose life span is longer and so on The ones that are very slow to show any effect are the bone cells, the nerve cells, etc , as they are already mature and do not undergo much differentiation or cell division following irradiation. We could spend several hours discussing the law of Bergoni and Tribondeau, but in general, I think you would find the statement to hold that those tissues and cells which are going to show a radiation reaction first, are those more often involved with cell division at the time of irradiation.

One has to distinguish between ionizing irradiation and ultra-violet which is not ionizing. Among the various types of ionizing radiation, one has to distinguish between low voltage x-rays, high voltage x-rays, beta rays, gamma rays, betatron rays, and others that lay people and even the medical students have heard of, but are not sure as to what they mean. In general, we have to consider two different effects of quality (Fig. 5). If the

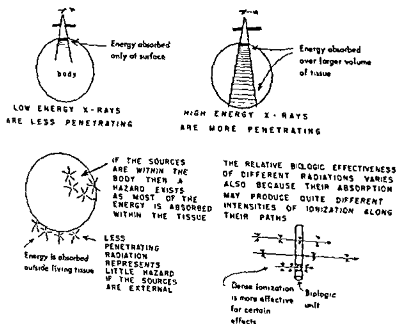



Figure 5

energy of the radiation is different, there is a different distribution of the energy in the body. It is pretty difficult to have the same distribution in the body with low energy x-rays that you have with high energy radiation Low energy x-ray effect is shown, in the upper left, as far as depth dose is concerned You can see that very little of it gets to the deeper part of the body, whereas in the case of high energy radiation, the energy is distributed over a larger volume. Thus, you have a different volume dose and a different geometry situation It is only where you have the same

Quimby on skin erythema, they found that by fractionating the dose, they could prolong the latent period for the appearance of radiation effects and that more radiation could be given in these fractionated exposures to produce the same effect. It is known from animal experimentation that the effect of dividing the exposure into a number of small ones greatly decreases the acute and also the sub-acute reactions. It may not decrease the delayed effects so much, but it certainly does reduce the more acute reactions.



























*Figure 1*

(Fig. 4) This slide demonstrates the response in the different tissues If we are interested in early reactions, we will see these in tissues that are rapidly growing, such as the epithelial cells and the blood cells. Those intermediate in response are the ones that are intermediate in reactivity to things in general, the ones whose life span is longer and so on The ones that are very slow to show any effect are the bone cells, the nerve cells, etc , as they are already mature and do not undergo much differentiation or cell division following irradiation We could spend several hours discussing the law of Bergoni and Tribondeau, but in general, I think you would find the statement to hold that those tissues and cells which are going to show a radiation reaction first, are those more often involved with cell division at the time of irradiation.

such as "dominant" and "recessive," etc. We inherit from both parents. We inherit two possibilities—you might say two comparable genes—one of which you use. The other you simply carry along. It is very evident that some inherited characteristics will show up more often than others. In other words, they are the dominant ones. In this diagram, the dominants are capital and the recessive are small letters. Consider two individuals, both heterozygous (in other words, there is one dominant and one recessive in each parent) each produce two different kinds of germ cells—one with a dominant, the other with a recessive gene. When the two dominants come together, of course, the individual is going to have a dominant character. It will be homozygous for dominant. There will be two others that are heterozygous. They will appear to be black haired or brown eyed or whatever the dominant character is. One out of the four, if you have enough children (in fruit flies, this holds more definitely) would have the double recessive showing up. In the case of radiation effects, you simply are increasing the rates of mutation. You are increasing the frequency with which abnormalities or unusual characteristics are produced. Like radiation itself being in our environment and being in all of us, the occurrence of mutations is a natural one. There is a natural mutation rate for humans and radiation exposure increases this frequency. So far as I know, and I have read this in many genetic papers there is no way to determine whether a particular mutation has been the result of ionizing radiation or the result of some other factor. All you can tell between two experimental groups is that one has a higher frequency than the other. Now sometimes the dominant character is lethal and will kill hte offspring either in the very early stages or in later stages of development. On the other hand many mutations are recessive as shown in the lower right, and such a mutation will not die out right away. In fact, it will not show up right away and might never show up at all, but continue to be carried until eventually it occurs in a double number or unless it occurs in the absence of a dominant gene which situation would allow it to express itself.

I believe that these are the important points to know in talking to nurses, to technicians, or to the public. We do not like the

geometry and the same dose distribution that you can discuss the relative biologic effects of these two different radiations in a strict sense. In a gross way, you can compare them. You can even compare the effects of x-rays with the effects of some internal emitter like inhaled radon or some other radioactive material that gets inside the body. If it is an alpha emitter, although the alpha particles would not penetrate the skin, once they're inside and in the mucosal lining of the lungs, for example, or in the bone marrow, all of their energy is going to be absorbed right in living tissue and is very effective.

In the lower right (Fig. 5) is a diagram of a chromosome. Photo-electrons possessing enough energy can plow through tissue or cells to produce ion pairs that are far apart as shown in the upper one and in the one just below it, too Down at the bottom of the chromosome, are tracks produced by slowly moving particles which are giving up their energy in a very dense pattern so that several ion pairs may take place in a very small part of the chromosome This makes it more effective in some cases, but in other cases, where only one ion is necessary, then the others would be wasted. This is the basis for the relative biological effectiveness of different radiations in the strict sense On the other hand, there is the general or practical sense of the term in which you can compare the relative effectiveness of any type of radiation There is a tendency to differentiate these two by speaking of the strict definition as relative efficiency and the gross as relative effectiveness I am not sure whether these terms will continue to be used.

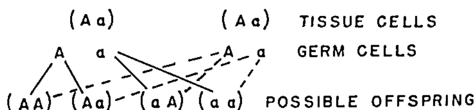



Figure 6

Just in case the geneticists do not talk in simple terms, Fig. 6 is to remind the radiologists that we are talking in genetic terms,

rather than the genetic or gene mutation probability theory for the induction of cancer. The genetic theory that tumors are the result of somatic mutations, (mutations in tissue other than germ tissue) is very popular at the present time.

(Fig. 7) This demonstrates the effect of heavy irradiation on the epiphysis of a bone. As a child, this patient was irradiated for a lesion of the knee. It was known at the time that it would



Figure 7

affect the growth of the bone, but in medical practice, one always has to balance the good against the bad. That is our problem today--to discuss ways whereby we can reduce the exposure as much as possible to use the radiation in the most efficient way, and, to continue to take the great advantages it offers in diagnosis or treatment of human ills

idea of trying to settle the scientific facts by public opinion, but scientists as well as politicians have thrown us into this and we have to face it now. We have the problem of trying to talk about technical problems to lay people and it's not easy but we have to do it ourselves or get someone else to do it.

Now, I would like to discuss briefly the historical development of radiation protection procedures and some of the clinical terms which will be helpful to the geneticists.

By an "acute reaction" we mean one that appears rapidly, is very harmful and comes on very soon after a large exposure to radiation. There is edema or swelling which is followed by necrosis or formation of large areas of dead tissue.

"Erythema" is a reddening of the skin. This biologic reaction was noted in the early days even before we had x-ray dosimeters and certainly long before we had pocket chambers and film badges that would measure exposures quantitatively. Some of you might be surprised to know how long we have had regulations for controlling radiation exposure. They were started even before we had the physical exposure unit, the "roentgen." Exposures were regulated in terms of milliampere-minutes at a certain voltage and with a certain filtration. These exposure times were based on their ability to produce an erythema and so the first exposure regulations were in fractions or multiples of erythema units. As the methods of measuring radiation exposure improved the maximum acceptable levels of radiation exposure were lowered. Not all of the credit for the lowering of acceptable levels of exposure can be attributed to pressures from various scientific groups or committees. I think that quite a bit of it has been a logical development paralleling improvements in the methods of measurement. Whenever it has been found that it would be practical to lower the acceptable limits, it has been done.

Histologically, when the skin is irradiated with a very heavy dose, we see (1) epilation, or a loss of the hair follicles, (2) an increase in fibrous tissue and (3) what appears to be a compensatory hyperplasia of the epidermis. In many cases we see, histologically, compensations or overgrowths resulting from insults. The histopathologist would probably favor the physiological

effect? The interesting thing is that there does seem to be an almost proportional relation between the daily dose and the reduction in survival time.

Fig. 15—Collection of alpha emitters in the lungs.

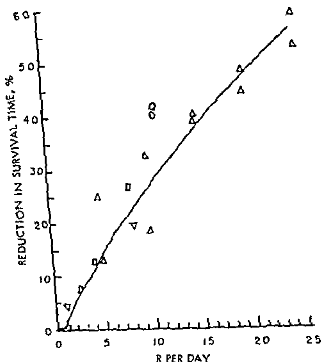



Fig 16—Effect on longevity of the amount of daily irradiation.

Figure 9

When a biologist talks about tumor production, it has to be understood that usually he is working with animals of a particular strain Perhaps it is one that has a high frequency of tumor incidence already. It is much easier to produce more leukemia in a strain that already has leukemia than it is in one that is resistent. We are not always very clear to point this out, but it must be kept in mind. For example, in one experiment at 0 dose (these animals

(Fig. 8) This is an example of a chronic effect resulting from many repeated small exposures. This dentist used his thumb and forefinger to hold dental film for his patients. Today, the well informed dentist does not do this, but years ago protective measures were not taught in the dental schools. We have known about radiation effects since the very early days, yet, somehow, it has not been kept as a consistent subject in the teaching of dental and medical students We seem to forget about it until some damage appears, then it is emphasized again. It needs to be given a definite place in the curriculum so it can't be left out.



Figure 8

(Fig. 9) Here is another effect, the delayed effect from fractionated exposures of so many roentgens per day I compiled these figures from my own data and from that of the others on the life span in mice who received different amounts of radiation exposure per day One does not know just where to draw the line. Does it go to zero or is there a threshold above which you get an

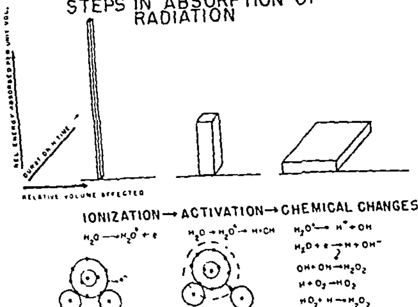



Figure 10

absorption per unit as does the primary events. This carries on to chemical changes in which the processes are spread over a large volume and results in recombinations to produce such toxic materials as hydrogen peroxide and others When a radiation change is not affected very much by protraction or fractionation, we think that this must be related to an early step, such as ionization, or the primary process One of the biologic effects that seems to fit th s condition is the increased frequency of gene mutations. These are inherited changes and you cannot see any chromosome abberations to account for it so we think that it is due to a point mutation On the other hand, chromosome aberrations might be due to this primary process or they might be due to this second one, perhaps a little farther along because the dose effect curve shows a little bit of a threshold It s more S-shaped There is a little more of a change if you fractionate or protract and it is a little more affected by temperature oxygen and other environmental factors

happened to be exposed to neutrons) there were 37 out of 100 that had one tumor, four that had two. Thus a small increase in number of tumors per animal following irradiation was not very significant. This strain was susceptible to lung tumors If you considered lung tumors alone and if you considered only those that appeared early in the life of the animal, there appeared to be a great increase in the incidence of lung tumors in the irradiated animals But when you consider the data for the entire life span of the animal, there were actually no more tumors in the irradiated group than in the controls. The tumors came on earlier and had I stopped the experiment in three months, I would have concluded that the induction of tumors was much greater, when actually it was an acceleration. Also you will hear statements that the production of tumors is directly proportional to dose and this again is all right in the sense in which the biologist means it However, if you carry it to the extreme, it doesn't hold because at the high dose of 1.4 r. per day, only fifteen of these animals had tumors where as the controls had 37. Just to look at the data like that you would say, "Well, radiation would reduce the number of tumors." It didn't. What it did was to kill them before they had time to develop a tumor, so these things can't be carried to an extreme when they talk about proportionality

The last diagram (Fig. 10) is designed to demonstrate the mechanisms of how I think radiant energy produces biologic effects Starting at the left, I have three ordinants One, the amount of energy absorbed per unit volume (energy-ergs per cubic mm); the next ordinant is duration of time and the horizontal one, the relative volume effect. The first thing that happens is that a photon knocks out an electron and this photoelectron then produces ionization This initial event is one which represents the absorption of a lot of energy in a very short period of time but doesn't affect a very large volume The next step is that each of these ions has the ability to interact with other atoms, perhaps to activate them to cause the electrons to move with a little higher velocity so that radicals may be produced This activation or excitation process lasts longer and spreads over a larger volume of protoplasm although it doesn't represent as much energy

# MECHANISM OF RADIATION DAMAGE TO LIVING TISSUE

*By*

GEORGE H. MICKEY, Ph.D.

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I should like to preface my remarks by stating that although I am a geneticist, I think that radiology has been a great boon to mankind The judicial, proper, and careful use of x-rays are highly desirable. My own interest in the effects of radiation go back for many years — some thirty years now. I was associated with Muller and Patterson and some of the others who were working at the University of Texas in the early days. In fact, I used the same x-ray machine that Dr Muller did when he irradiated the flies in 1937 and came up with his famous paper. Geneticists have not always been as cognizant of the dangers of radiation as they appear to be at the present time I remember back in the early 1930's, one of the graduate students at the University of Texas went into the attic where this x-ray machine was located It was not shielded by lead or anything It was sitting out in the middle of the attic room where it was operated. There was a little lead booth over in the corner where the operator sat and watched the instruments Dr. Patterson had some flies under the x-ray beam that he was busily irradiating This graduate student happened to come up and found him sitting there by the unprotected x ray tube, and he said, "Why, Dr. Pat, don't you know what this will do to you?" And he said, "Why, sure, but I'm all through anyway"

Irradiation damage is always a calculated risk. As Dr Evans said, you always have to compare the expected damage to the expected good which will result from it My interest, of

This brings us to those effects which are definitely altered by the environment, such as the amount of oxygen, the temperature, etc. They probably act in a later process more like the chemical changes produced by other toxic agents in the body.

I could go on and on, but I think I've done enough to introduce Dr Mickey's talk on "The Mechanism of Radiation Damage to Living Tissue."

## FIGURE REFERENCES

Figures 1, 2, 3, 4, 5, 6 and 9 are from a paper entitled: *Effect of Ionizing Radiation on Mammals and its Implications for Accelerator Shielding* by E. C. Evans, at Conference on Shielding of High-Energy Accelerators, New York City, April 11 to 13, 1957.

Figure 7 is from an article by Frantz, C. H., entitled, "Extreme Retardation of Epiphyseal Growth from Roentgen Irradiation," from *Radiology*, 55 720-721, 1950.

Figure 8 is from an article by Hultberg, Sven, Larrson, L. E. and Eklund, E., entitled *Some Cases of Radiation Injury in Radiology Work*, from *Acta Radiologica*, 33 376, 1950

speak of as somatic or pathologic damage. According to this classification, the genetic damage may be defined as changes wrought in the germ cells either in the mature sperms from the male or the mature eggs from the female or in the earlier germ cells in the gonads which give rise to these definitive gametes. Even here, sensitivity varies according to the stage of development of the germ cells. For example, the spermatids, that is, those male germ cells which have undergone the several mitotic divisions and the two meiotic or maturation divisions and are undergoing the metamorphosis into the mature sperm, are considerably more sensitive than some of the other stages These alterations in the germ cells, whether they are gene mutations or chromosomal aberrations (that is, the chromosomes are broken and reunited in various ways), can be transmitted to the progeny and thus are inherited or passed on to future generations.

Many different kinds of mutations are known from experiments with a great variety of plants and animals. For example, we may speak of dominant and recessive mutations, as has already been pointed out to you, affecting visible characters or traits in the individuals These are commonly referred to in genetics as visibles In other words, a kind of a mutant that shows up as a morphological or a physiological change in the organism, we call a visible They may be further characterized as either sex-linked or autosomal The sex-linked mutations are the result of changes in genes carried on the X chromosomes or the sex chromosome, whereas, the autosomal mutations are in genes which are located on any of the other chromosomes besides the sex chromosomes

Then, of course, there are the mutations which have been referred to as lethal mutations That is, those which interfere so drastically with the normal development or functioning of the cells that they result in the death of the organism. Most of these lethal mutations have their effect early in the life cycle. That is, in mammals it might occur in the egg or in the embryo or in the fetus, or if we're talking about some other organism, an insect for example, it might occur in the larvae or in the pupae or even in the adult Most of them have early effects These, too, we may

course, has been in the basic, or fundamental biological aspects of the problem — the way in which these ionizing radiations will affect the cells. As Dr. Evans has already explained, ionizing radiations damage living tissue regardless of the source, whether it be external or internal, and regardless of the specific kind, whether x-rays, gamma rays, alpha or beta particles, protrons, neutrons or cosmic rays. Even ultra-violet is damaging to living tissue if it reaches that living tissue. As you know, the ultra-violet is not ionizing radiation, but it does excite material, and it has low energy. It has a long wave length and it doesn't penetrate very far. Therefore, it affects only the surface tissue of the skin. But if one gets the ultra-violet to living cells, say for example in tissue culture, and irradiates them, one can see the effect of it. It is very powerful in fractionating or fragmenting the chromosomes of the cells Ultra-violet can do this if it reaches these chromosomes.

There are many factors, some of which will be discussed by Dr Herskowitz, that control the degree of damage. Among them, of course, are innate or genetic differences in the biological organisms themselves. In other words, even among human beings you will find some people that are far more susceptible to the effects of x-rays than others; 600 r of whole body irradiation delivered in a single dose will result in the death of practically all the invididuals that receive such a dose, whereas, 450 r. of whole body irradiation is considered to be the LD 50 That is, it will kill approximately 50% of the individuals that receive such a whole body irradiation at a single dose Furthermore, various tissues, again as Dr Evans pointed out, will exhibit different sensitivities to the same amount of irradiation The blood forming elements are perhaps the most sensitive with as little as 25 r of whole body irradiation resulting in a detectable change in the blood picture. Whereas other tissues can withstand a great deal more with no apparent damage, for example, brain, liver, bone cells, etc. — not the red bone marrow but the bone cells themselves

Radiation damage has been classified in two general categories One of these we call genetic damage and the other we

speak of as somatic or pathologic damage. According to this classification, the genetic damage may be defined as changes wrought in the germ cells either in the mature sperms from the male or the mature eggs from the female or in the earlier germ cells in the gonads which give rise to these definitive gametes. Even here, sensitivity varies according to the stage of development of the germ cells. For example, the spermatids, that is, those male germ cells which have undergone the several mitotic divisions and the two meiotic or maturation divisions and are undergoing the metamorphosis into the mature sperm, are considerably more sensitive than some of the other stages. These alterations in the germ cells, whether they are gene mutations or chromosomal aberrations (that is, the chromosomes are broken and reunited in various ways), can be transmitted to the progeny and thus are inherited or passed on to future generations.

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designate as sex-linked or autosomal, depending upon the chromosomes which are involved. Since by far the great majority of mutations are recessive, they may be transmitted to the progeny of the individual in whose germ cells they occurred and may be carried in the heterozygous state. That is to say, these so-called recessive genes are covered up or hidden or obscured by the fact that there is a normal gene, an allelic gene which is normal and this normal gene can perform the function satisfactorily so that the recessive gene does not express itself phenotypically. They may be carried for many generations before they make themselves known or become expressed since these genes must be disseminated in a population sufficiently to have two such heterozygous individuals mating before the genes become homozygous and thus, show up This is why the germinal changes resulting from radiation may exist in the human population for as long as 500 to 1,000 years before cropping out. This is one reason why it is ridiculous to look at the progeny of irradiated people such as those of Hiroshima and Nagasaki and conclude that because few mutations appear in the first or second generation, that little or no damage has been done. Likewise, it is folly to conclude that since no monsters are observed in one or two children of a woman who has been irradiated with x-rays to induce ovulation, that no mutations have resulted from the treatment. This is a false assumption. In the first place, certainly you do not expect a monster in all genes of all cells and therefore, in order to detect them, you require a large number of progeny Furthermore, it is possible that a few of these mutations that may have resulted will be lethals which will eliminate the individuals before birth, and you are simply not aware of it. This point would bear further discussion, but that is all the time I can spend with it at this moment

We have mentioned the chromosomal abnormalities By these we mean that the chromosomes within the nucleus are broken and they may reunite in the original way without any genetic effect or they may reunite in many different ways, producing abnormalities or aberrations When they fuse together in

certain fashions, they produce the kind of aberrations that we refer to as translocations – that is, the part of one chromosome broken off and tied onto another; or inversions, which means that a portion of the chromosome is broken out and turned end for end and tied back into the chromosome again; deletions or deficiencies, which mean that parts of the chromosomes are broken out and lost; or duplications wherein portions of the chromosomes are found more than the number of times expected This constitutes a whole area of study in itself; that is, chromosome breakage and reunion and so on, and the facts involved here are quite intricate It might be that a little later on, I shall have the opportunity to mention some of these factors, but at this stage I shall pass over them quickly.

I should mention that the word "mutation" is used in a rather loose sense by the geneticists. We use the word both as a verb and as a noun We also use it in the sense to mean a point mutation or gene mutation, in which there is a change in the molecules that constitute a gene – that is, a point mutation Or we also use it in a broad sense to include the chromosomal aberrations, because the expressed effects in an individual sometimes cannot be distinguished between a point mutation and a chromosomal aberration Oftentimes when the chromosomes are rearranged, we have what is known as a positive effect and this effect resembles that of a gene mutation

Many of the so-called dominant mutations and also many of the lethal mutations are the result of chromosome breaks These are less likely to survive, that is, they are apt to be eliminated from the population more rapidly than the gene mutations are For instance, a sex-linked lethal mutation, even if recessive, will be eliminated in a male that receives such a gene since the male has only one X chromosome and has no normal counterpart to carry the individual through Thus, sexual reproduction serves in part to prune out such lethals

Let us consider now the somatic or pathological changes, those alterations occurring in cells of the body outside of the gonads in any of the tissues other than the gonadal tissue. As

pointed out by Dr. Evans, these are most likely to be expressed in tissues that are growing rapidly in which the cells are undergoing rapid cell division. This is due in part at least to the fact that the broken chromosomes in sex cells cause irregularities in the distribution of the genes and chromosomes to their daughter cells, thus creating the duplications and deficiencies which we mentioned earlier, resulting in the loss of some vital functions. They can no longer carry on normal metabolism. It is true that chromosomes can be broken and chromosomal abnormalities can occur in so-called resting cells; that is, cells which are not rapidly dividing. It is true that these breakages can occur in such radioresistant cells as nerve cells or bone cells or any other non-dividing cells in the body, but as long as these cells do not divide, all of their genes, or essentially all of them are retained in the same cell and can continue to function properly even if a recessive point mutation or gene mutation is produced. This mutation is likely to be obscured or hidden by its normal allele in that same cell since these cells are diploid, that is, they have two representatives of each chromosome and the probability of producing identical mutations in both homologous chromosomes simultaneously is practically nil. However, if such a cell subsequently divides, even weeks or months or years later, the damage can become evident. This explains, in part at least, one of the most insidious features of radiation damage, that is, the delayed effects, the latent period The delayed effects of irradiation have been known for a long time. Often it may be two to twenty years after treatment that cancer or leukemia results from excessive treatment. A few cases have been recorded in which a delay of as much as forty years has been observed.

As to the mechanism by which living cells are damaged, we may classify it in two categories first, the direct effect, and secondly, what we call the indirect effect

The direct effect means that an ionization has occurred within the molecule of the gene or chromosome and results in a chemical change. These direct hits are more likely to result from heavy particles such as alpha rays and neutrons and so on.

The indirect effect results when ionization occurs in the immediate vicinity of the chromosome or gene, resulting in the formation of charged particles or free radicals and these in turn set up a chain of reactions which eventually involve the genes or chromosomes within the nucleus of the cell. Such changes must be considered genetic, too, although not in the same sense that we mentioned earlier, since they are not in the germ cells and cannot be transmitted to offspring, at least in organisms which reproduce sexually; although it is possible, of course, for somatic mutations to be transmitted in such organisms as plants where the germ cells are produced on any branch of the plant. They are genetic in the sense that the hereditary units of the cell (that is to say the chromosomes and the genes within the nucleus) are involved Exposure of the body to the maximum permissible dose of radiation, which is .3 r. per week, directly disrupts about three hundred molecules in each of the one hundred forty trillion cells in the human body. A dose of 1,000 r., which would kill a human being, directly disturbs only about one molecule in ten million. Obviously, the changes induced among these relatively few molecules must become enormously amplified. How does this come about? Well, we do not know the precise answer to this question, but we do know the general pattern of radiation damage in cells The cells in the body are mainly water, and it is in the water that the primary effects of radiation take place. It is largely concerned with the production of free radicals. When water in the cell is acted on by radiation, a small fraction is decomposed into extremely reactive fragments called free radicals which readily interact to form peroxides and other cell poisons. These peroxides as well as many other decomposition peroxides can move around for a short while until they alter a receptive molecule. Among the most sensitive substances in the cell are enzymes which are essentially large protein molecules, and one enzyme molecule modified may transform a 100,000 or more molecules which are needed for the continuation of the metabolic activities of the cell Consequently, we have here one of the necessary multiplication mechanisms for transforming a relatively small radiation effect into an eventual observable injury to the

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also been studied) it it indicated that there is no threshold level below which mutations cannot occur. The point mutations are directly proportional to the dose received, whether it is in fractionated doses or whether it is in a single dose.

Recent studies suggest, although conclusive evidence is not yet available, that perhaps the same is true even for somatic tissues. If this is true, it means that no cell truly recovers from a dose of radiation, somatic or germinal. While a cell may seem to recover, there is an irreversible effect on the chromosomes and genes As in the case of hereditary traits, these somatic mutations may take many cell generations of a given cell type to manifest themselves. Sometimes the mutations may confer upon the affected cell and its descendants the property of more rapid growth than their neighboring cells Such cells may multiply rapidly, apparently not restrained by influences which inhibit the growth of normal cells As a result, the continuing growth becomes abnormal and is classed as cancerous. Where white blood cells are involved, of course, we speak of it as leukemia.

In many cases the effects of radiation are produced in cooperation with disturbances in body function in general One of these disturbances, the hormonal inbalance, can in itself aid and abet the cancer producing effects of radiation. This of course is an indirect effect It does not appear to be the direct result of irradiation but it is tied in with it For example, in mice as little as 50 r to the gonads depresses the production of the sex hormone This in turn stimulates the pituitary to form excessive amounts of the gonad stimulating hormone and in such mice the incidence of tumor is raised considerably There are many other points which I should like to touch upon, but I am sure that I have used all the time allotted to me

*Dr Paul Hodges* I have one question I would like to ask You made the statement, I believe, that it is possible for tumors to be produced as long as forty years after irradiation that are traceable to that irradiation What proof is there for that? How can one trace an individual tumor back that far?

*Dr Mickey* The case that I'm thinking about is reported by two doctors. A woman who was irradiated on the skin for a

cell. Similar analyses can be applied to single genes since these hereditary units presumably function through the production or elaboration of enzymes. Thus, radiation can harm cells by producing changes in the cellular environment. The cells are bathed by solutions from which radiation produced activated products reach and damage them. The poisonous product released by radiation-killed cells can circulate in the blood to other tissues; so, although we do ordinarily invision the damage to be directly on that tissue which has been irradiated, nevertheless this radiation damage can spread to a certain extent through the transportation of these poisonous toxic substances from the point of damage to other portions of the body

The response of tissues depends very much on the rate of delivery of radiation. The short range effects of radiation from sources as gamma rays, x-rays or beta rays are dependent upon the intensity of irradiation and the duration of exposure. Somatic damage to cells other than the germ cells may be repaired in part if broken doses or fractionated doses are given, but this does not apply to mutations produced in the germ cells These mutations are not repaired. Once they are produced, they remain and they can multiply or reproduce themselves in the altered states must as well or essentially as well as they did in the original state. For here the mutation rate is essentially directly proportional to the dose regardless of the rate or intensity. The dosage is cumulative This is why it is so important to shield or protect the gonads from radiation

Furthermore, experimental studies with many different organisms indicates that there is no threshold level with respect to these mutations That is, there is no level below which damage is not induced. Now I realize of course that this statement cannot be absolutely and unequivocably established, but particularly in those organisms where we can carry on extensive experiments, and working with low levels of radiation you have to have a very extensive experiment in order to detect the difference between that and the controlled rate. These have been carried out primarily in Drosophila In these organisms (incidentally, in rather rapidly producing organisms such as bacteria they have

through about ten years of study at the University of Indiana with him We will now hear from Dr. Irwin Herskowitz on "The Biological Factors Affecting Radiation-Induced Mutation Frequencies"

lesion that showed immediate effects of over-irradiation. This appeared to heal but at that same site (and of course this is arguable whether it was actually the result of it) a tumor did occur forty-nine years later. This is one case.

*Dr. Paul Hodges:* This is a skin tumor related to a skin damage.

*Dr. Mickey:* That is right.

*Dr. Hymer Friedell:* I'd like to point out that unquestionably a tumor appeared, and I don't think there is any reason to challenge this, but to interpret that this necessarily is due to somatic or genetic changes in the cell is very difficult because you can injure the cells in other ways and produce tumors. Therefore, all that one could really say is that injury occurred and a tumor resulted. Whether this is due to the specific effect on the genes, the somatic genes, or some somatic effect of some other kind, I think would be very difficult to establish.

*Dr. Mickey:* I readily admit this. There is no question but what there are many factors which enter into the picture, but I think that the so-called mutation theory of cancer explains only one type of damage which may result in cancer.

*Dr. Evans:* In case you've been wondering why I speak to George (Dr. Mickey) so familiarly, he and I were students back in Baylor University many years ago, and I also became acquainted with Dr. Muller, although I didn't work with him. I knew of his work and I think this influenced my interest in radiation biology a great deal. In fact, I was invited as a student by a friend of mine who was a doctor to attend a meeting of McClennan County Medical Society at one time at which Dr. Muller talked about his experiments. This, I think was in 1927, or 1926, and he told the radiologists at that time that radiation would affect the genes and would increase the mutation frequency and that radiologists should be very careful about it. Of course, there was a tremendous discussion thereafter. Points were brought out that there was quite a difference in fruit flies and humans and so on. But it was very interesting that many of the points that night are still being discussed today. Some with more assurance and some with less assurance. Dr. Muller has also influenced our next speaker,

single file, like the beads on a string. There are probably as many as 2,000 genes along the length of an average human chromosome. Since the chromosomes in all cells but the mature egg and sperm occur in pairs, so do the genes they carry.

Typical chromosomes have three parts: two ends, two arms and a specialized region that is needed for transporting the chromosome into a daughter cell after division. Any permanent loss or change of these parts will involve the genes located therein and is called a *mutation*. Usually only one chromosome takes part in a mutation while the others present are unaffected. So, in a cell with paired chromosomes an unchanged chromosome with its unchanged genes is usually present when the other member of the pair has mutated.

Permanent changes that involve whole sections of genes can result after the chromosomes are broken in one or more places. These broken ends can join to other broken ends in pairs, each union being permanent once it occurs. If the broken ends from the same break rejoin, there will be no change in the number or position of the chromosome pieces. But if the pieces combine so the genes are arranged in a new order, the result is called a *gross chromosomal rearrangement*. So long as a cell containing a gross chromosomal rearrangement does not divide relatively little damage results. If, however, this cell divides, then, depending upon the type of rearrangement, one of the two daughter cells may have a whole section of rearranged genes missing while the other daughter cell has this section *in excess*. As a result the nicely balanced gene content of the normal cell is upset and the daughter cells cannot function properly, or die.

Not only are there mutations involving whole sections of genes as just described, but there are those which involve a very localized region of the chromosome, containing perhaps only one or a few genes. These minute changes in chromosomes are called *point mutations*. As already mentioned by Dr. Mickey, there is no good evidence that a minimum dose of radiation is required to produce a point mutation. When people talk about the amount of natural radiation being acceptable, they do not mean that such radiation fails to produce its share of mutations

# FACTORS AFFECTING RADIATION-INDUCED MUTATION RATES

*By*

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Before discussing some of the factors which influence the production of mutations by radiation, it may be profitable to review briefly the basis and nature of human inheritance. This is easily done at the cellular level. Each cell, as you know, normally, contains a nucleus which is in turn filled with bodies called *chromosomes.* While viruses and other materials outside the nucleus may be transmitted from a parent cell to its two daughter cells after a cell division, it is primarily the chromosomes which transmit the hereditary material from one cell to another In this way heredity produces two human cells from the division of one human cell.

The great majority of people probably have 46 chromosomes in each tissue cell of their body, these chromosomes being composed actually of 23 pairs. One set of 23 unpaired chromosomes was contributed by our mother and the other set of 23 by our father when we started life as a fertilized egg Subsequent cell divisions produced a baby and later an adult, each of whose body cells carries 23 pairs of chromosomes. In each mature sex cell of the adult, however, as a result of special series of cell divisions, there is only one set of 23 chromosomes. Moreover, each of the 23 unpaired chromosomes carried by a mature egg or sperm has an equal chance of being one that came originally from the mother or from the father of the individual forming the sex cell

Along the length of each chromosome are the smallest particles of inheritance, the *genes*, lined up one behind the other in

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between ion pairs and clusters of them, on the one hand, and mutations on the other. Unfortunately, we do not have any radiation that produces clusters composed of a single ion pair with a big space in the tissue before another ion pair is produced, and so on. Had we such a ray we could determine whether only a single ion pair is needed to produce a point mutation.

Ionizing radiation like x-rays produces clusters which probably range in size from those with only one ion pair to others containing a hundred. A typical x-ray cluster is *composed* of more than one ionization pair. With a given quality of ionizing radiation one obtains a range of cluster sizes and upon lowering the dose this range does not change. Suppose with a low dose no more than one cluster occurs in a nucleus. This probably is true when 20 r of x-rays are delivered to Drosophila (fruit fly) sperm. Assume in this case 20% of the sperm have one cluster in them, and that each cluster has, on the average, 12 ion pairs in it. If the dose is reduced to 5 r one will not get 20% of cells having a cluster containing only 4 ion pairs. One would get 5% of the cells having a cluster of 12 ion pairs. Dosage experiments down to about 50 r have shown in Drosophila that the point mutation rate is proportional to the dose. If the doses were further reduced so only one cluster occurred in a nucleus at the higher one (and hence at the lower dose, too) one would almost surely find that the point mutation rate was linear to dose. That is, point mutation has no threshold, or safe, dose. Should dosage experiments down to 5 r be performed, they would involve considerable technical difficulty because the radiation-induced effect would be small and very careful large-scale controls would have to be run. Most geneticists feel that all the way down to zero-r point mutation rate will be proportional to the amount of x-radiation received, being at these low doses proportional to the number of nuclei containing a cluster.

Not only do we not know how many ion pairs are required to produce a point mutation, but we do not know exactly how many are required to break a chromosome. A point mutation is attributable to the action of a single cluster of ionizations and the cluster which produces it may or may not have also

They understand that this amount is unavoidable and since one cannot do anything about it, the consequent damage is accepted Any additional radiation, this may be more or less than the natural amount, will also cause cellular damage and produce mutations. This is the part society may be able to avoid by keeping the added radiation exposure to a minimum. And one of the main purposes of this symposium is to discuss this problem.

If one considers the nature of the energy that stays in tissue after treatment with ionizing radiation it is found that the energy left is not entirely in the form of ionization. (We measure the amount of tissue dose only in terms of ionization when we use the roentgen as the unit ) The roentgen is not the best measure of the relation between absorbed energy and mutation production. This is so because mutations are produced not only by the ionizations (which act on the genes directly, or indirectly via some nearby nuclear material like water) but they are produced also by energy left in the nucleus in the form of excitations or activations which make compounds more reactive chemically and, therefore, more likely to interact with genes. In the case of x-rays or gamma rays, however, probably only about one-sixth of the energy is left in tissue as activations, the rest as ionizations. Geneticists are interested in the answer to the question, "How much of the energy of other kinds of radiation is left in tissue in the form of ionization and how much as activation?"

We need to know more about the ability of non-ionizing energy to produce mutations With ultra-violet radiation all of the mutations are produced through activations Accordingly, more basic research on the study of ultra-violet-induced mutations will be fruitful. We also need to have more physical studies on the distribution and the form of ionizing energies left by different wave and particulate radiations As already indicated by the two previous speakers, we simply do not know enough For instance, what is the spread of the ionization in tissue for different kinds of radiation? More specifically, what are the sizes of the clusters of ion pairs produced and how are these clusters distributed relative to each other? Once we have accurate data on these matters, we can study better the relationship

were produced. This would leave the pieces from the second break no alternative to join other than in the original arrangement. So, under these conditions, lower x-ray intensity would produce fewer gross rearrangements. This illustrates why the dose and the intensity of x-rays play an important role in the production of two-break gross chromosomal rearrangements. If x-ray tissue damage is dose or intensity dependent and has a genetic basis, it is almost certainly due to gross rearrangement

This dose-intensity dependence for x-rays does not obtain, however, for mature sperm of animals, and probably of humans, also For in these cells the broken pieces cannot join to each other and are therefore accumulated For this reason, it makes no difference how fast or slow a dose is given to the chromosomes in a sperm head The breaks remain unjoined until fertilization, when the sperm head swells and the broken ends are permitted to join in pairs So much for the discussion of certain physical aspects of penetrating radiation and their bearing on mutation production

In discussing the biological factors which affect the frequency of radiation-induced mutations several questions must always be kept in mind. How do these agents act on the chromosome breakage process, and how do they affect the ability of the broken pieces to join to others? It is usually difficult, unless carefully designed experiments are performed, to tell whether an agent is affecting the breakage or the rejoining phenomenon, or both It should be mentioned that no agent is known which can break a chromosome yet not produce point mutations, or the reverse of this

There are several ways that the gene content of the cell itself influences radiation-induced mutation rate We know that there are genes whose presence increases x-ray susceptibility of the cell to mutation Alternative genes can decrease this cell sensitivity, perhaps operating by decreasing the likelihood of breakage and or by increasing the likelihood of broken pieces rejoining in their old position

Another genetic factor is involved when an organism or cell has extra chromosomes. In one case, there might be one extra

produced a break in the chromosome in the same or a nearby region. Therefore, point mutations sometimes are and sometimes are not located at a point of exchange of a gross chromosomal rearrangement. We do know, however, that some radiations which produce large clusters are in some ways relatively inefficient and wasteful of ionizations. These densely ionizing rays produce a smaller percentage of cells with gross chromosomal rearrangements than is produced by the same dose of a radiation having smaller cluster sizes, that is, where the ionizations are spread out more. Here then is one measure of relative efficiency of different radiations for the production of mutations.

Certain types of gross chromosomal rearrangement, already described by Dr. Mickey, require two breaks for their production. When a neutron enters a nucleus it produces ionizations in clusters which are large and close together. Because of this concentration the ionizations can pass through one chromosome at two different places or through two different chromosomes, so that a gross rearrangement, even though it required two separate breaks, can be produced by the passage of one particle through the nucleus Thus, the frequency of two-break gross rearrangements following neutron radiation increases linearly with dose and is independent of the rate with which the dose is delivered. If a less densely ionizing type of radiation is used, like x-rays, the clusters are smaller and spaced farther apart. Here, two breaks in the same nucleus are usually produced by two separate clusters, one having no dependence upon the other for its origination For this reason many x-ray-induced gross rearrangements are dose and intensity dependent For when a low dose is given, a nucleus could contain only one cluster and could produce only one break. The dose would have to be raised high enough to get cases of two or more breaks per nucleus For these rearrangements, then, there is a threshhold, or safe, dose for x-rays. If a larger x-ray dose is given in a short interval, two breaks could be produced in the same nucleus simultaneously and could result in rearrangement But if the same dose is given more slowly, then the pieces of the first break could join to form the original gene arrangement before those from the second break

ent mutation rates for genetic reasons Thus, for example, a species with more genes will have more point mutations produced in it for a given dose, and one with more chromosomes will have more gross chromosomal mutations of certain typees. This may be part of the reason why an organism like the fruit fly, which has only four pairs of chromosomes, and perhaps 10,000 genes, is relatively less mutable than a species like man, with 23 pairs and maybe 50,000 genes

Other biological factors which can influence mutation rate are known which are not based so directly on the kind of number of genes or chromosomes, although these may be influenced by genes One of these concerns the spatial arrangement of the chromosomes relative to each other. When the chromosomes are packed into a tight ball of threads like they are in the tiny head of the sperm, a different picture is presented for breakage and later rejoining than when the chromosomes are spread throughout a large nucleus For if they are spread out the ionizations of a small cluster or from a penetrating particle are unlikely to break chromosomes twice Even in those cases where two breaks do occur in a large nucleus, the pieces will be frequently too far apart to interchange, and the result will be that those which join will usually form the original gene order

Even within the same sized cell there are a number of other biological factors which can influence breakage or rejoining. These include the presence of a restrictive and insulating nuclear membrane, the degree of spiralization of the chromosomes, the stress or tension under which the parts of a chromosome are held, the degree of hydration and the amount of chromosome matrix in which the gene string is embedded, protoplasmic viscosity and the amount of movement around the chromosomes [illegible]

[illegible] where the members of each chromosome pair come to lie close to each other, as they do at a certain stage in sex cell formation For under these conditions the forces which keep like parts of one chromosome apposed to the like parts of the other member of the pair may prevent the pieces

set of chromosomes present, so instead of two sets three are present. The number of point mutations per cell caused by a given radiation dose will be proportionately increased (by 50%) by the presence of the extra set. While more point mutations would be produced the damage caused to the cell carrying these would probably be less per mutation than to a normal two-set cell because there would be present two sets of normal genes and chromosomes to counteract the effect of the mutation in the third set. On the other hand, it can be shown that gross chromosomal rearrangements, and much of the damage they produce, would be increased by more than the proportional amount expected due to the addition of an extra set of chromosomes. These expectations need to be taken into account also in cases where certain cells or individuals have one or two chromosomes more than others, a situation known to exist among humans.

Within the same individual, one can find various cells with different chromosome numbers. For instance, human mature sperm and eggs have only one set of chromosomes, that is, 23, while the normal cell has twice this number, or 23 pairs. A typical cell which is just about to divide will have its 23 pairs of chromosomes exactly doubled and so it will be expected to be especially radio-sensitive. This is true also during certain stages in the maturation of sperm and egg cells. In addition, one can find, within the liver, cells which have more than two sets of chromosomes.

Differences within and between individual chromosomes also can modify the type or rate of radiation-induced mutation. It is known that some parts of a chromosome are more likely to undergo breakage and rearrangement than others. Certain point mutations are induced more frequently than others by radiation. This does not mean that one can selectively produce a specific type of mutation by radiation, but that amongst a large number of induced mutations certain ones crop up more frequently than others. This demonstrates, another way, that the genetic content of the individual modifies mutability.

Not only can there be genetic differences in mutability within an individual or a species, but different species can have differ-

of broken ends, thereby decreasing the opportunity for chromosomal rearrangement

The action of many physical, chemical, and biochemical agents in modifying the mutation rate can be partly understood in terms of an effect on oxygen concentration during or after x-radiation This includes the effect of respiratory enzymes which increase or decrease oxygen concentration and of agents which poison these chemically (including metals which are involved in enzyme construction or inactivation), chemical substances which release oxygen (such as inorganic or organic peroxides), pH, and temperature (at lower ones more oxygen is dissolved) Certain normal biological phenomena may themselves produce or involve changes in oxygen concentration, such as the biochemical events which accompany cell differentiation, the presence or dissolution of the nuclear membrane, and the location of tissue relative to inter-cellular oxygen supply

It should not be thought, however, that the entire effect of oxygen is explicable in terms of a single patch of action either for breakage or for joining, since a number of the biological factors mentioned must be also dependent upon oxygen and the mutation effect must in some cases result from modifying these. One should also realize that although much of the modifying effect of biological factors can be attributed to effects on oxygen certain of these agents influence mutation rate by other means For example, temperature is known to modify mutation rate apart from its relation to the solubility of oxygen X-rays produce more gross chromosomal rearrangements when treated oocytes are previously dehydrated This may be so because the oocyte nucleus is shrunken, causing the pieces from different breaks to be located closer together, proximity of broken ends favoring interchange, and acting contrary to the radioprotective action which removal of water frequently provides

In summary an attempt has been made to describe briefly certain intrinsic characteristics of penetrating radiation which cause differences in mutation rates, as well as to indicate some of the biological and non-biological factors which can influence the ability of ionizations and activations to produce mutation.

newly produced by breakage from moving apart freely, the unbroken chromosome strand serving as a splint for the broken one. This would serve to reduce the opportunities for cross union between ends from different breaks. All these factors determine to what degree the pieces produced by a breakage may move or spring apart. Those which change the distances between different chromosomes or the parts within a chromosome will also affect chromosome breakability.

On the biochemical level there is a very simple system which greatly influences the number of point mutations or the number of breaks and their joinability. This involves water and the oxygen dissolved in it. X-rays produce very reactive (hence short-lived) chemical ions from both, as already described in some detail by both Drs Evans and Mickey. Not all radiation-induced mutations have their basis in ions from oxygenated water, however, although a good many of them do. Those with this origin have a pathway from the radiation to the gene that is indirect.

Consider next the specific role of oxygen in radiation mutation. If a normally oxygenated cell is x-rayed a certain number of chromosomes will be broken. When the amount of oxygen is reduced the same dose produces fewer breakages, and when the amount of oxygen available is increased above the normal amount somewhat more mutations are obtained than under normal conditions. The presence of oxygen during irradiation, therefore, promotes chromosome breakage. It also increases the frequency of point mutations. It is also known that once a break is produced the presence of oxygen permits or promotes the joining between broken ends. If oxygen is absent or reduced after a break is produced the pieces are not able to join together. Under this condition broken ends are saved up, until oxygen is restored, at which time the cell may contain pieces from many different breaks. These can then join in rearrangements that would not have been possible had the dose been given slowly in the presence of oxygen when a given piece would have had fewer opportunities for cross union. From the standpoint of gross chromosomal mutation, therefore, oxygen has two opposite effects: it increases the number of breaks but promotes the early rejoining

*Dr. Crow:* Dr Herskowitz has been talking about radiation-induced mutations, which because of the oxygen effect may have a negative temperature coefficient, whereas mutations from other causes seem to have a positive coefficient. If this is true in man, then the testes will have a lower mutation rate than if they were internal and at a higher temperature.

*Dr. Gould:* One may cancel the other then.

*Dr Crow:* Possibly. However, it is probable that the majority of mutations are not due to radiation. Thus, the most likely effect of a decreased temperature would be a decreased mutation rate

*Dr Scott:* Is there any basic difference in normal cells and malignant cells in these things you've been talking about?

*Dr Herskowitz:* There is probably a genetic difference It always amuses me to hear someone say: "See, there's a malignant cell! You can tell it's malignant because it has a tripolar spindle, or because you see a chromosome lagging, or because you see broken ends" That's not the malignant cell That's a dead cell or it's going to be a dead cell The real malignant cell, the one that is going to divide and produce more cancer cells, is the one which is apparently not very much abnormal chromosomally. Many people think that cancer cells differ from normal cells, however, by a number of point mutations Surely, it's true in some cases that point mutations are responsible for initiating tumors

*Dr Mickey:* The major difference, I think, between the malignant and the normal cell would be in the rate of cell division, and the more rapidly these cells are dividing, the more susceptible they are to irradiation damage

*Dr Brues:* May I just question the statement that the malignant cell divides more often than the normal cell There are very few [illegible]

as cells in [illegible]

*Dr M[illegible]* [illegible] that statement would apply to such cells as well as to the malignant tissue, that is to say, these embryonic tissues are just about as susceptible to irradiation damage as are the malignant cells.

*Dr. Evans*: Is there any question you want to ask before Dr. Herskowitz leaves?

*Dr. Gould*: I was wondering how much of a difference in the mutation rate there would be with a cell in a resting phase when the chromatin is spread around the nucleus and differences between prophase, telephase or the various phases.

*Dr. Herskowitz*: I'll take a guess Fourfold.

*Dr. Gould*: It could be fourfold.

*Dr. Herskowitz*: Yes.

*Dr. Gould*: And it's most sensitive in which phase would you say?

*Dr. Herskowitz*: The metaphase is supposed to be most sensitive. Say, for instance, you irradiate oogonia which are in all stages of nuclear division and obtain a certain mutation rate. If a colchicine treatment precedes the radiation many of these cells will be kept in metaphase and the mutation rate would be increased several-fold Modifying factors produce an effect on mutation rate which is of a different order of magnitude than is the effect of radiation itself For while radiation can produce a thousandfold increase over the normal mutation rate, some modifying factors described may cut the rate down to only a five hundredfold increase. Thus, while the effect of modifying factors may be very appreciable, the protection they may afford may be only a relatively small percentage of the total damage by radiation.

*Dr. Gould*. One other question — you said that when the temperature is decreased, more oxygen becomes available to the cell.

*Dr. Herskowitz*: It is not dissolved

*Dr. Gould*: More is dissolved, and therefore, the mutation rate will be increased.

*Dr. Herskowitz*: Right.

*Dr. Gould*: How does that jibe with the Swedish point of view that the reproductive cells of the testes are at a lower body temperature than the reproductive cells of the ovaries?

*Dr. Herskowitz*: You would expect a slightly higher mutation rate per cell, at the lower temperature.

*Dr. Crow*: Dr Herskowitz has been talking about radiation-induced mutations, which because of the oxygen effect may have a negative temperature coefficient, whereas mutations from other causes seem to have a positive coefficient. If this is true in man, then the testes will have a lower mutation rate than if they were internal and at a higher temperature.

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*Dr Brues*. May I just question the statement that the malignant cell divides *more often than* the normal cell. There are very few tumors whose cells grow as rapidly as embryonic cells or as cells in regenerating tissues or in intestinal epithelium

*Dr Mickey*: But that statement would apply to such cells as well as to the malignant tissue, that is to say, these embryonic tissues are just about as susceptible to irradiation damage as are the malignant cells.

*Titus Evans*: Well, I hate to stop this, but we must go on with our talks now and withhold our discussion until each speaker has had a chance to get over his main points. Now our next one is Dr. William Russell and I am sure that most of you know that Dr. Russell has been engaged in a tremendous project with enormous numbers of mice, and he is going to tell us about the radiation induced genetic damage in mammals.

# RADIATION-INDUCED GENETIC DAMAGE IN MAMMALS

By

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Dr Evans mentioned the large mouse colony we have I might point out that if these mice were Drosophilae, you could contain them all in half pint milk bottles occupying probably about half of one table top here. So don't expect wonders from mouse genetics because of large numbers They take up a lot more space than Drosophilae, and our mouse laboratory could compare to a very small Drosophila laboratory.

I thought I might briefly discuss 18 points that I prepared for a recent summary of mammalian radiation genetics. A few of these are basic things that were discovered in mammalian genetics some time ago and which our work has confirmed We have found others that I think have a very direct practical application to the question of genetic hazards of radiation in man And still others undoubtedly will have a practical application, sooner or later, but, at the present time, they are fundamentally of pure biological interest

(1) The first point deals not with a genetic effect, but actually with damage observed in the testis following irradiation The findings in this field have important implications for interpretation of the genetic damage Dr. Oakberg in our group has found, by careful quantitative estimates of the amount and type of damage in the testis, that one-half of the spermatogonia are actually killed by a dose of 22 r of gamma rays, and he can measure the amounts of killing, with statistical significance, down to (with the size samples which he used, which are not enormous)

*Titus Evans*: Well, I hate to stop this, but we must go on with our talks now and withhold our discussion until each speaker has had a chance to get over his main points. Now our next one is Dr. William Russell and I am sure that most of you know that Dr. Russell has been engaged in a tremendous project with enormous numbers of mice, and he is going to tell us about the radiation induced genetic damage in mammals.

The bulk of the dose will have been received in the spermatogonial stage. Similarly, if you are exposed to an acute dose at one time from an accident or medical treatment, it is unlikely that you will actually have a fertile mating within the five or six weeks immediately following irradiation. In such cases, you usually know that you have been exposed anyway and can refrain from procreation for these few weeks after irradiation. Thus, here is the one place in mammalian radiation genetics where some of the risk can be controlled, at least with regard to chromosomal aberrations. However, even if we don't try to control these, they may still not be a very important hazard

(3) The preceding point has concerned chromosomal aberrations induced in males. We turn now to females Oogonia are not present in the adult mammal, certainly not in the mouse and probably not in the adult human female. All germ cells in the mouse are in the primary oocyte stage, i.e., they have already passed out of the oogonial stage. And here, chromosomal aberrations could conceivably have turned out to be a hazard because the gonial stage, from which radiation-induced aberrations are not recovered in the male, has been irrevocably passed in the adult female However, it was shown in our work (this is Mrs Russell's work) that with females, as had been found with males, dominant lethals cause death extremely early in development About 60% of them are detectable in the two-cell stage of the embryo, and practically all of the deaths due to dominant lethals occur before implantation, or at the time of implantation, or very shortly afterwards. Thus, although dominant lethals *are* induced in females, they would not cause much grief in a human situation (The same consideration applies, of course also to dominant lethals induced in males )

(4) Unlike dominant lethals, translocations are not weeded out early in development and are passed on to descendant generations, causing particularly semi-sterility in the offspring These translocations as already mentioned, are induced in post-spermatogonial stages *but* are not induced in the spermatogonia A possibility still existed that they might be induced in the oocytes of the female but here we found an extremely low rate. Only one

as low as 5 r of gamma rays and even with 2 rep of neutrons. Now, these are the cells in which we are primarily interested from the point of view of genetic effects. From these measurements, which are made *in vivo* and not in tissue culture, we find these cells to be extremely sensitive. In contrast to this, the testis does recover from tremendous doses of irradiation in mice. We can give 1000 r of acute x-ray exposure to the testis and the males will return to fertility. In fact, with a good hybrid stock to start with, there is no difference in the percentage of animals that is finally fertile: less than 1% are sterile, both in the control and exposed groups. Thus, some of the spermatogonia are apparently extremely resistent to killing. We have, then, these two very clearly defined different types of cells among the spermatogonia: and this, as I will mention later, does have a bearing on our interpretation of the genetic effects observed.

(2) As earlier work has shown, and our work has confirmed, most chromosomal aberrations, induced in males, are found only in the offspring conceived in what we call the presterile period, which in our experimental work means shortly after irradiation That is, the chromosomal aberrations recovered in the offspring are those that have been induced in post-spermatogonial stages (the spermatocytes possibly, spermatids definitely and sperm definitely), which occupy only about five weeks in the development of mature sperm from spermatogonia. In this short interval after irradiation, one does find a high incidence of chromosomal aberrations — dominant lethals, translocations, and so on — in the offspring But, so far, a statistically detectable increase in these aberrations caused by irradiation of spermatogonia has not been really firmly established The actual hazard from this type of genetic effect is, therefore, I think, small in man where the radiation dose received by a male germ cell in its post-spermatogonial stages will usually be negligible compared to that received in the spermatogonial stage For example, if you are exposed to chronic irradiation over a long period of time, since it takes only five or six weeks for the spermatogonia to mature, then only the small dose received in later stages will be important for the production of chromosomal aberrations

tists, is that mutation rate is linearly related to dose. On the other hand, some pathologists would tend to think that the mutation rate is not linearly related to dose and that there may be some threshold mechanism involved, or that the two-hit processes may be more important than is thought and that the mutation rate would not be as high at the lower doses as you would expect on the basis of simple linearity Our results have actually revealed the possibility that the mutation rate might be higher at lower doses To explore this third possibility, we performed a mutation rate experiment with 300 r and, so far, the results are not out of line with the rates obtained at 0 and 600 r The actual 300 r rate is, it turns out, a little bit higher than the value derived by interpolating between 0 and 600 r, but not significantly so The fact that the 300 r rate is a little higher than expectation again raises the question of whether, at still lower doses, the rate might not be higher still Low dose experiments of course take an enormous amount of work, but we have approximate data for an 86 r dose at the present time This dose consisted of gamma rays given chronically, while the radiation in the 300, 600 and 1000 r experiments I mentioned consisted of acute x-rays. Thus, the experiments are not exactly comparable, and this may turn out to be important As it stands, the rate at 86 r from chronic gamma rays is actually below the 300-to 0 interpolation This, of course, has only limited meaning because, due to the small yield of mutations at this low dose, the confidence limits are still wide at the present time What we can definitely conclude, however, is that the upper 90% limit is less than twice the value derived by interpolation between the 0 and the 300 r acute x-ray rates This is reassurance that, at low doses, we are not going to have a fantastically higher mutation rate than that estimated by interpolation

*Question* What is the rate at which this 86 r is delivered did you say?

*Dr Russell* About 10 r per week for a period of between eight and nine weeks

(7) We come now to possible differences between chronic and acute irradiation With 516 r of chronic gamma radiation,

translocation was picked up in over 300 offspring examined for this particular anomaly, which is a very much lower rate than occurs in postgonial stages of the male. The conclusions from Drosophila work apparently apply directly to the mammal in this case: a very low translocation rate has been reported for Drosophila females.

(5) We now turn from major chromosome aberrations to so-called point mutations. Here I might mention some rather recent work which may not even be known to many geneticists: the x-ray induced mutation rate in spermatogonia of mice shows a departure from the linear relation with dose at higher doses. At 1000 r, the mutation rate actually drops down. Now, this departure from linearity is the reverse direction from that which would be expected if two-hit processes were involved, i.e., chromosomal aberrations involving two separate breakages, that situation would tend to make the line curve upward as the dose increased. The departure actually observed is in the other direction. A plausible hypothesis is that this may be due to differential sensitivity among the spermatogonia. Thus, at the higher doses, we may be killing a high proportion of more sensitive spermatogonia, and, if there is a correlation between their sensitivity to killing and their mutation rate, then at the very high doses we may have just the mutation rate that is left in the more resistant spermatogonia. As I say, this is just a plausible hypothesis at the present time. At least it is borne out by the histologically observed differential sensitivity among the spermatogonia.

(6) As a sort of corollary of point (5), I think the possibility is not yet excluded that the mutation rate per roentgen at lower doses and intensities may actually be higher than that so far estimated from the doses we have used. If differential sensitivity of the spermatogonia is the explanation for the drop in mutation rate between 600 and 1000 r, then possibly at doses below 600 r, where perhaps we have all the sensitive cells left, we might have a mutation rate higher than the 600 r rate. I should like to emphasize this a little bit because it is contrary to two common notions about genetic damage. One, held by geneti-

cists, is that mutation rate is linearly related to dose. On the other hand, some pathologists would tend to think that the mutation rate is not linearly related to dose and that there may be some threshold mechanism involved, or that the two hit processes may be more important than is thought and that the mutation rate would not be as high at the lower doses as you would expect on the basis of simple linearity Our results have actually revealed the possibility that the mutation rate might be higher at lower doses To explore this third possibility, we performed a mutation rate experiment with 300 r and, so far, the results are not out of line with the rates obtained at 0 and 600 r. The actual 300 r rate is, it turns out, a little bit higher than the value derived by interpolating between 0 and 600 r, but not significantly so. The fact that the 300 r rate is a little higher than expectation again raises the question of whether, at still lower doses, the rate might not be higher still Low dose experiments of course take an enormous amount of work, but we have approximate data for an 86 r dose at the present time This dose consisted of gamma rays given chronically, while the radiation in the 300, 600 and 1000 r experiments I mentioned consisted of acute x-rays. Thus, the experiments are not exactly comparable, and this may turn out to be important As it stands, the rate at 86 r from chronic gamma rays is actually below the 300-to 0 interpolation This, of course, has only limited meaning because, due to the small yield of mutations at this low dose, the confidence limits are still wide at the present time What we can definitely conclude, however, is that the upper 90% limit is less than twice the value derived by interpolation between the 0 and the 300 r acute x-ray rates This is reassurance that, at low doses, we are not going to have a fantastically higher mutation rate than that estimated by interpolation

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(7) We come now to possible differences between chronic and acute irradiation. *With 516 r of chronic gamma radiation,*

given at the rate of 90 r per week, the mutation rate is unexpectedly low when compared with the results of 600 r of x-rays given at 80 r a minute. The intensities of radiation in the two experiments differ by 4 orders of magnitude. The results at 516 r, in conjunction with the limited data at 86 r total dose, raise the question of whether chronic irradiation might give a lower mutation rate than does acute in the spermatogonia of the mammal.

*Question*: Excuse me. What kinds of changes are you referring to?

*Dr. Russell*: I should have mentioned these. We measure what we call specific locus mutations. We have reason to think that major chromosomal aberrations are not involved when we irradiate spermatogonia — and all data I am talking about now concern spermatogonia. In irradiation of mature germ cells, on the other hand, results are complicated by the production of chromosomal aberrations, some of which appear like specific locus mutations.

*Question*: What do you mean by specific locus mutations?

*Dr. Russell*. Just a mutation restricted to the place (locus) occupied on the chromosome by a particular gene.

*Question*: Give an example of what you see — is it a hair color?

*Dr. Russell*: Yes. Five of the seven we look for are hair color changes, one is white-spotting, and the seventh one is a short-ear mutation. Mutations at these seven loci that have occurred spontaneously in the laboratory in the past were built into a specific "test" stock We irradiate the stock *not* carrying these mutations, mate to the "test" stock, and look for repeats of these *particular kinds of mutations in the first generation offspring*. As far as we can tell, these repeats are gene mutations, or, strictly speaking, "point" mutations, since it is impossible, at the present time, to prove that we are not dealing with very minute deficiencies, i.e , losses of chromatin material involving the locus or its immediate adjacent region. However, there is very good evidence that such deficiencies, if they occur at all in spermatogonia, must be extremely small

To return to point (7) The idea that chronic irradiation

might be genetically less effective than acute, is of course, heresy among geneticists, so one looks for other possible explanations of the results. Well, one possible explanation is that we are causing more damage to the testis with chronic irradiation than we were with acute and that, following only 516 r chronic gamma, we may have a situation similar to that postulated for 1000 r acute x-rays, i e, a mutation rate that characterizes resistant cells. In any case, until we have more evidence on this point, I think it would be risky to jump to the conclusion that chronic gamma irradiation to spermatogonia in mammals will give less mutation than acute x-rays However, this possibility is now, I think, worth exploring considerably. I have a private view on this, but I won't state it at the present time

(8) The three preceding points have, I am sure, indicated the complexities in the relation between mutation rate, dose, and dose rate. You see, we have found two departures from the generally accepted genetic concept, i e, (a) drop in the mutation rate at 1000 r of acute x-irradiation, and (b) the lower mutation rate following chronic exposure than following 600 r acute x-rays. In view of these observed complexities and other complications that occur when we are dealing — not with a uniform population of sperm — but with the spermatogonia, that are going through cell division all the time, and are known to have differential sensitivity to killing, I think the best thing we can do at the present time is to take the highest mutation rate so far obtained in the mouse, namely, that in the 300 r experiment with acute irradiation, and use this for estimates of damage in man. The induced rate in the 300 r experiment, if you want an actual figure is $28 \times 10^{-8}$ per r, per locus This rate is many times higher than that found in comparable experiments with Drosophila. There have been a number of statements that man is not a Drosophila and that his mutation rate may be much lower than the Drosophila rate But now an organism which is a good deal closer to men, the mouse, actually goes in the other direction: the mammalian mutation rate seems to be considerably higher than the Drosophila rate

(9) Points 5-8 have concerned specific locus mutations in-

duced in males. We have a little data also on the mutation rate in offspring of irradiated female mice. It is difficult to do acute experiments in female mice because they become permanently sterile with even a low acute dose. Thus, even 50 r sterilizes after four litters and one needs, in general, higher doses than this to make an easy experiment. However, we have some work in progress in which females were given 258 r chronic gamma irradiation at the rate of about 86 r per week, and here fertility persists almost as long as in controls, at least long enough to get a large number of offspring And again the mutation rate is low. Now in the female gonad we are not dealing with a population of rapidly dividing cells: oogonia are not present in adults, and oocytes remain in a constant condition apparently throughout life until just before ovulation. Consequently, the low mutation rate cannot be explained on the same hypothesis as that suggested to explain the drop-off found in males at high acute doses, or following chronic application of the dose Thus, it appears that the mutation rate in females may be really low and not spuriously low, if you want to use this term This raises, I think, considerable hope that this finding may also apply to the human ovary exposed to chronic gamma irradiation. We can't speak of acute x-rays because we don't know the results, and this leaves considerable uncertainty as far as medical exposures are concerned, because fractionated acute doses may give a genetic effect more like that of the single acute dose than that of chronic gamma irradiation given continuously.

(10) There is no evidence of significant recovery from genetic damage with time after irradiation. I think Dr. Mickey *mentioned* this for Drosophila, but, for various reasons, this point needed to be established afresh in a mammal The earlier evidence for lack of recovery came primarily from dose fractionation studies in Drosophila, but this work was all on mature sperm Now there were (or so it seemed to us at least), very definite possibilities for recovery, when one was dealing with spermatogonia instead. Supposing the induced mutation itself actually *affected* the rate of cell division of a spermatogonium Then it would lose out in competition with other spermatogonia and, a

long time after irradiation, the mutation rate might drop, as the probability of recovering a mutant sperm derived from this particular spermatogonium would decrease. We felt that, in view of this possibility, it required very definite experimental work on spermatogonia, and also in a longer-lived organism than Drosophila, and also, I think, in a testis that is histologically similar to man (rather than being quite different in anatomy and physiology as in the Drosophila testis) to re-establish the principle of lack of recovery. Well, we have looked at this carefully enough, I think, to say that there is no significant difference in the spermatogonial mutation rate a short time after irradiation and a long time after irradiation. So there is no evidence that would allow us to count on recovery from genetic damage with time.

(11) The mutation rates of the seven loci in our sample vary markedly from each other. Thus, there is a factor of over 30 between the lowest rate and the highest rate in spermatogonia. These differences tend to disappear when you deal with the radiation of mature sperm, and I think this is probably due primarily to the contribution of other chromosomal aberrations which give effects simulating the specific locus mutations

*Dr Mickey:* I'm sorry I missed a point there. Do you mean the differences of the different loci? Is that what you were referring to?

*Dr Russell.* Yes, the *A*-locus, for example, has a very low rate and the *S*-locus has a very high rate and the difference is *more* than thirty-fold in a sample of only 7 loci

*Dr Mickey.* Excuse me. You're speaking of the radiation-induced mutation rate?

*Dr. Russell.* Yes, I'm speaking of radiation-induced mutation rates

*Dr Mickey:* It occurs spontaneously, *too*

*Dr Russell:* Well, it's well known, of course, with spontaneous rates, e g , in maise, that the variation among loci is tremendous Much bigger differences than this *occur.*

*Dr Mickey:* Are these in the same order when you look at the spontaneous *rates?*

*Dr Russell* The number of spontaneous mutations, un-

fortunately, is not extensive enough yet to answer this. There is such a low spontaneous rate, when you deal with specific loci, that we can't conclude anything definite, so far.

*Dr. Mickey*: May I inject the studies of Stadler on maize? He has shown this particularly with specific loci spontaneous rates in corn.

*Dr. Brues*: What is the correlation between radiation-induced mutation rates and spontaneous rates?

*Dr. Russell*: As I have mentioned, we have just a handful of spontaneous mutations so nothing definite can be decided at this time.

(12) A point that I've already touched on lightly is that deficiencies commonly found among mutations induced in post-spermatogonial stages have not been found, so far, in the cases recovered from irradiated spermatogonia. In specific locus mutation experiments on irradiated sperm, further analysis of certain of the specific locus mutations reveals that they are not point mutations or gene mutations, but are caused by a small piece of the chromosome having been knocked out of this particular region. The same criteria applied to mutations induced by the irradiation of spermatogonia reveal no such sign of deficiencies. This is part of the supporting evidence that most mutations induced in spermatogonia are point mutations, and that they may even be gene mutations.

(13) There are also significant differences, among the seven loci explained, in the proportion of the mutations that turn out to be recessive lethals. At two of the seven loci, for example, all of the mutations that were detected by their visible effect on coat color turned out to be lethal in homozygous condition, that is, when the mutation is brought in from both the mother and the father, in a descendant generation, those offspring receiving it in double-dose fail to survive. Lethals have been induced in all loci, and the total proportion is quite substantial. At least half of all the mutations recovered are completely lethal. This is, I think, an unbiased result because, when we started the experiment not a single lethal mutation was known at any of the seven loci that we picked for a study.

(14) In contrast to what Dr. Mickey reported, most of the recessive lethals tested in our experiments do not fall into the category in which death occurs so early in the embryos as to pass unnoticed in human experience. On the contrary, they kill at times that I think would be tragedies in human experience. All the lethals at one locus kill at about weaning age, which is about three weeks of age in the mouse. Not a single mutation at this locus kills earlier than this At the other of the two loci that have given nothing but lethals, most of the mutations (in homozygous condition) apparently kill at about the time of birth. Thus, these recessive lethals induced in the mouse are quite different from many recessive lethals known in Drosophila and also quite different from the dominant lethals induced in the mouse which kill in the early stages of development.

(15) Some of the lethals induced in the mouse have so strong a dominant deleterious effect that it is actually apparent in the individuals carrying them in heterozygous condition. That is, the lethal, when homozygous (inherited from both parents), will kill the individual; if inherited from only *one* parent, it has an *effect* on body size so marked that you can actually see it without weighing the individual. These heterozygous individuals *may* be affected in other ways as well: e g, it is probable that their life is shortened.

(16) Other mutations in heterozygous condition, *i e.*, inherited from only one parent, have *effects which* are not apparent in the individual *but which* are discernible statistically. *Thus,* the viability of offspring of irradiated animals is reduced, as compared with *the controls* I think it is quite important that we find out more about these statistically *detectable* heterozygous effects, because, if the mutations *which are* completely lethal in the homozygote have a slight deleterious effect on the heterozygote in the human situation, *then* the heterozygous effect will probably be far more important, from the point of view of hazards, than the complete lethality of the homozygote. The reason for this will, I expect, be discussed by Dr. Crow, so I will leave it to him.

(17) One way in which we *have* measured the heterozy-

fortunately, is not extensive enough yet to answer this. There is such a low spontaneous rate, when you deal with specific loci, that we can't conclude anything definite, so far.

*Dr. Mickey*: May I inject the studies of Stadler on maize? He has shown this particularly with specific loci spontaneous rates in corn.

*Dr. Brues*: What is the correlation between radiation-induced mutation rates and spontaneous rates?

*Dr. Russell*: As I have mentioned, we have just a handful of spontaneous mutations so nothing definite can be decided at this time.

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*Question:* Wouldn't this be an important difference whether the litter size was diminished or whether they actually were born viable and then died?

*Dr Russell.* Yes. We have tried to determine this but it would take a tremendously large-scale experiment to break down further something that is only 3-4% to begin with. We have some indication from what we have done that at least some of the deaths occur after birth. Thus, here again it is not all death before birth. My guess would be that, since we are presumably dealing with a point mutation type of effect here, we probably have to look for slight shifts in statistical distributions, i.e., if an animal carries a certain mutation, it will increase his probability of dying before a certain age. Not every animal that carries this mutation will die, of course.

*Question.* By litter size here, do you mean the number of offspring or the total weight?

*Dr Russell.* The number of animals per litter.

(18) Perhaps our most definite direct measure of damage in the descendant generations was established about a year ago from an experiment that was set up primarily to maximize the effect. We found a very striking *shortening of life* in the offspring of the exposed individuals. This includes the whole life-span – not just that up to three weeks of age: in fact, deaths before three weeks of age were excluded from the analysis. In this experiment, in which irradiation was done with neutrons, we found 0.6 days shortening of life per rep of neutron irradiation given to the *father*. Translated to man (by simply assuming that life shortening would be the same proportion of the total life span, which probably is not justifiable, but gives a rough idea) this means about twenty days shortening of life per rep. of neutrons received by the father. Now I must emphasize that the effect was maximized in this experiment, on several counts. First of all the relative biological effectiveness of neutrons may be greater than unity for this effect. Secondly, this was not a spermatogonia experiment: irradiation was given to more mature gametogenic stages, probably spermatids, which, as Dr Herskowitz has already mentioned, are very sensitive genetically. It

gous effect is by relative survival to three weeks of age in the large specific locus experiments. I use this particular age because it is then that we kill all the animals if they don't show specific locus mutations, and we, therefore, have large numbers of animals raised to three weeks of age. Survival to this age in the first *generation descendants of the irradiated animals* is *lower than* in the controls. The difference is not big — with 300 r we get about 3 or 4% reduction in survival to this age — but it has turned up in every single experiment that we have done, and if you break down the 300 r experiment, for example, into ten successive groups, you will find about the same difference in each of the ten successive groups. There is, I think, no doubt that we are dealing with a real reduction.

*Question*: Are these the children of parents that have been irradiated or are the children themselves irradiated also?

*Dr. Russell*: These are the offspring of males that were irradiated. You simply observe the litter size at three weeks of age and you find that it is reduced in the group where the male has been irradiated, as compared to the control group where the male has not been irradiated.

*Question*: The children themselves were not irradiated in this three-week period?

*Dr. Russell*: No, they were not irradiated. The same, of course, is true of the other heterozygous effects mentioned, reduction in size and so on.

*Question*: Does the litter size diminish, too?

*Dr. Russell*: Well, survival to three weeks is actually measured by litter size. I call it survival to three weeks of age because when you talk about litter size, people usually assume this means at birth. Actually, these animals are not looked at until they are three weeks of age, the reason for that being we have to go through such tremendous numbers that if we looked at them twice, we would have to double the work and wouldn't recover many more mutations — *only those that have died in the interval* between birth and three weeks. So we have these large-scale experiments in which the animals are looked at at three weeks of age.

here. That is, in this experiment alone we have, over the years, looked at 100,000 mice to recover 100 or so mutations. Of course we have several other acute x-ray experiments in addition The mutation rate in the *chronic* experiment of 516 r is, so far, based on one mutation. You may recall that I spoke about a 600 r acute and also about a chronic experiment in which the rate was much lower. The 600 r acute rate is based on over 100 mutations. In the chronic gamma experiment, our estimate is based on one mutation in over 10,000 offspring at the present time, but, nevertheless, this is statistically a significant difference. That is, even the upper confidence limit of the mutation rate from chronic irradiation doesn't approach the higher rate. Thus, we have one mutation, where on the basis of the 600 r acute, we would expect about 12. This is a highly significant difference.

*Question*: One locus — maybe that would clarify it a bit. That is a specific type of mutation at this locus.

*Dr. Russell*: No, this is just one mutation in all seven loci

*Question*: And that was in how many mice?

*Dr. Russell* That was in about 11,000

*Question* How many mice did you irradiate with 600 r acute?

*Dr. Russell* Well, the number of offspring was about 120,-000.

*Question* And the number of mice irradiated?

*Dr Russell* I guess it must have been between 1500 and 2500

*Dr Evans*. I know you have a lot of questions, but we have some more talks and discussion before the noon recess We have asked two radiologists who have given this some thought to come in at this point The first one is Dr. Arthur Smith from the Research Hospital in Kansas City He is going to talk on the "Accumulative Dose Concept."

is, I think, desirable to maximize an effect in the early phases of experiments when one is trying to uncover whether something exists or not. We now have other experiments going along these lines. They are not complete yet, but two of them (employing x-radiation) are far enough along to show that the effect is in the same direction. As expected, it looks as though the effect will not be as big as in the neutron study, but it will probably add up to a significant shortening of life.

## SUMMARY

Let me give you a quick summary to help organize the seemingly disconnected points I have discussed. Most of our experiments (points 5-18) would fit into two categories One type, the specific locus experiments, have been conducted primarily to make comparisons: to compare mouse with fruit fly, to compare low doses with high doses, to compare intensities, to compare males with females, to compare mutation rate a short time after irradiation and a long time after irradiation Let me stress that all of these are comparisons They are not direct measures of the amount of damage expected, but they explore the factors which will affect the damage So little was known about the genetic effects of radiation in mammals that we felt these basic things had to be looked into first In the second category of experiments, which were not begun until recently, are those concerned with empirical measures of the actual damage Among these are studies of the effects of particular mutants that we have found, and, more important, population studies, such as the ones in which we found reduction in survival to three weeks of age or shortening of the whole life-span. All of these studies fall into the category of direct measures of damage.

*Dr. Scott:* Dr Russell, what kind of numbers are you talking about in your experiments, 10,000 mice or 100,000?

*Dr. Russell:* Well, in the 600 r x-ray experiment, the number of mutations, I think, was 111 in over 100,000 offspring examined. We got about one mutation per thousand offspring

and need only to discover ways in which to measure them precisely

Radiation can give rise to mutations in the genes. The majority of radiation induced mutations are harmful. The genetic damage done is roughly proportional to the total mutation rate. Any radiation dose, however small, can induce some mutations. Additional radiation, over and above the irreducible minimum due to natural causes, produces additional mutations over and above the spontaneous mutations The probable number of additional induced mutations occurring in an individual over a period of time is by and large proportional to the total dose of extra radiation received over that period by the reproductive organs where the germ cells are formed and stored To the best of our present knowledge, if we increased the radiation by X%, the gene mutations caused by radiation will also be increased by X% The total dose of radiation is what counts, based on the fact that the genetic damage done by radiation is cumulative A larger amount of radiation produces a larger number of mutations Within the limits of radiation doses being considered *in this report*, moderately larger doses of radiation would produce more but not worse mutants The concept of a safe *rate of* radiation does not make sense if one is concerned with genetic damage to future generations What counts from the point of view of genetic damage is not the rate It is the total accumulated dose to the reproductive cells of the individual from the beginning of his life up to the time the child is conceived What is genetically important to a child is the total radiation dose that child's parents have received from their conception to the conception of the child The significant total dose period should be approximately the number of years that normally elapsed from the conception of a person to the average time at which offspring are conceived. In the United States, *this is thirty* years, and this is also the figure usually chosen to measure a generation Using this 30 year figure for characterizing the "total reproductive life radiation dose," we have the result that about half the total offspring would receive *the possible* effects of a smaller and about half the possible radiation effects of a larger radiation

# ACCUMULATIVE DOSE CONCEPT

By

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*Research Hospital*
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I am going back a bit to the beginning to review some fundamentals on the accumulative dose concept. I am not sure it is completely accurate yet, but based on the NAS report, "Biological Effects of Atomic Radiation" and a little from Lee's book on the actual radiation on living cells, I am going to present this outline and hope that it is in agreement with the general terms that we have heard.

The science of human genetics has not yet advanced far enough to be able to give precise answers regarding the dangers of various levels of radiation. Naturally, there are some differences in opinion among geneticists themselves as to exact numerical values, although no disagreement as to fundamental conclusions.

Single celled organisms, as well as fruit flies and corn plants have been especially rewarding objects to genetic studies. In evolutionary terms, however, insects and plants are clearly a long way from man and we are just beginning to get genetic information about the effects of radiation on some of the lower mammals such as mice Even so, certain important matters have become clear. Bacteria or fruit fly, mouse or man, the chemical nature of the hereditary material is universally the same, the main pattern of the hereditary transmission of traits is the same for all forms of life reproducing sexually, and the nature of effects of high energy radiation upon the genetic material is likewise universally the same in principal Hence, in human genetics where the impossibilities of ordinary scientific experimentation are clear, we can at least feel certain of the general nature of the effects,

# SOME GENERAL ASPECTS OF THE DOSE RESPONSE CURVE AND ITS SIGNIFICANCE

*By*

**HYMER L. FRIEDELL, M.D.**
*Director, Department of Radiology*
*University Hospitals of Cleveland*
*Cleveland, Ohio*

There isn't any question that radiation produces certain delayed effects There are fairly well known and can be classified essentially into three broad categories. (1) mutations as a result of changes in the genes; (2) the production of certain special diseases, generally of a neoplastic nature, such as leukemia, and perhaps certain types of tumors, and (3) a general loss of vitality, one of the measures of which is decrease in longevity.

The first of these — mutations — produces effects in the offspring, the last two produce effects in the individuals. It has been suggested that the first is thought to be an effect on the genes, but it has been postulated that it is conceivable that the latter two may also be due to genetic changes, but these are genetic changes in the somatic cells rather than in the reproductive cells

These changes have been shown to be present at *high levels* of radiation. The question that must be answered is, *do these* same effects occur at lower levels of radiation, and if these occur at lower levels of radiation, what is the *character of the dose* response curve, and can one determine whether these effects are cumulative and non-threshold By non-threshold we mean that any level of radiation, however small, produces some effect

The best evidence that one could possibly obtain would be to establish the mechanism by *which biological* effects are produced by radiation, and until we know this mechanism clearly, there is not likely to be any complete understanding of the bio-

dose. In summary, it is not the radiation per se which accumulates, but the mutations produced by radiation continue on through one generation after another, and it is these mutations and their harmful genetic effects which are cumulative

At present, 2% of the total live births in the United States have genetic defects. If mankind were subjected to a doubling dose, say 30 to 80 r of radiation, this figure would probably increase by 10% in the first generation. On the above basis, a radiation dose of 10 r would give rise to 50,000 new instances of tangible inherited defects in the first generation. The effect of a given dose of radiation in producing mutations is independent whether it is concentrated into a short exposure at high intensity or is spread over a long time by fractionation or by the use of low intensity and I would say, of course, after listening to Dr. Russell, that that last statement probably is not true — that these things even as written are not as true as when they were written.

*Dr. Evans:* Thank you, Dr Smith. That was a very nice, concise presentation.

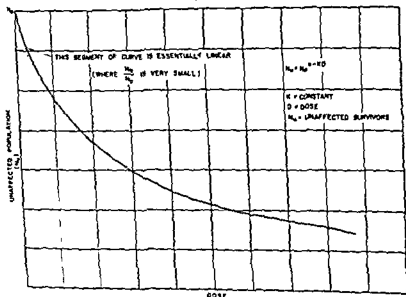
*Dr Pirkey:* I'd like to bring up a point apropos of what Dr. Smith said I'm just wondering if we should always say as he did in his talk, that all mutations are harmful because as I understand it, without mutations, we would still be amoebas. That is, if life began as a one cell organism in the sea, wouldn't we still be amoebas?

*Dr. Evans* We're getting into the realm of discussion, but we'll allow one answer here

*Dr. Crow* You are precisely correct If all mutations were harmful, we would still be viruses or whatever we originally were. It would be much more correct to say *almost all* Evolutionary progress depends on that small minority of mutations that are favorable.

*Dr. Scott* · Before Dr. Friedell begins his talk, you should know that it was his suggestion that led to the authorization for these Conferences. His advice and suggestions were most helpful in getting this meeting organized.

tracts $N_a$ from N and the equation becomes $N = N_o\ (1 - e^{-KD})$. As noted above, this is not mathematically a linear curve and is strictly semi-logarithmic. However, when the number of events that are occurring are very small compared to the possible total number of events, or the number of targets that are altered compared to the total number of targets is very small, this is essentially linear and it is permissible to plot the number of events directly against dose. (See Fig 1-a and 1-b.)




Lacking specific information as to the mechanism of *the pro-* [illegible]

[illegible] exists or not, and therefore whether the dose is cumulative or *not*. *It* should be pointed out that this is not unique for radiation effects alone, but applies *to* all biological studies where the dose is plotted against response It automatically means that if the curve is semi-*logarithmic*, it is, therefore, a single event function and it is very *difficult* to avoid the conclusion that there is no threshold and *that* the doses must be cumulative

logical effects of radiation, and at best will be presumptive and even conjectural. For the present discussion, the points that are critical are whether the effects are cumulative and whether or not a threshold exists.

From my observations, the basis for making such decisions has rested primarily upon the dose response curve and certain tests that can be made of this curve. I have, therefore, chosen to examine the character of the dose response curve and see what possible interpretations may exist Broadly speaking, the dose response curves may be looked at two ways — is it linear, or non-linear? The reason for making such a separation is that the linear curve (truly not linear and really semi-logarithmic — I will touch upon this later) indicates that the events that are occurring with respect to dose are independent of one another This may be termed a single event function, and variously referred to as the direct effect, the target effect, or single hit mechanism. The multiple event function means that a number of events must occur in order to produce a biological effect. This fits primarily with the concept of an indirect effect and is by far the most common process which is found in physiological data. The reason for stressing these two types of curves are essentially these. If the dose response curve is linear, there is a very strong possibility that the effects are non-threshold and cumulative. If the dose response curve is non-linear and appears to be a multiple event function, there is almost certainly a threshold and the effects with respect to additive doses cannot be completely cumulative As I noted above, generally a single event function is referred to as a linear curve Actually this is a semi-logarithmic curve in which the logarithm of the response is plotted along the y axis and the dose is plotted along the x axis. The equation for this is simply $N = N_0e^{-KD}$ (N are the events being observed, K is the constant, and D is the dose). This is a simple semi-logarithmic expression. It indicates that the number of unaltered units are decreasing If you are measuring mutations, it would indicate that the number of unaltered genes are decreasing In most instances, the dose response curves are plotted so that the effect is plotted against the dose and in this instance one simply sub-

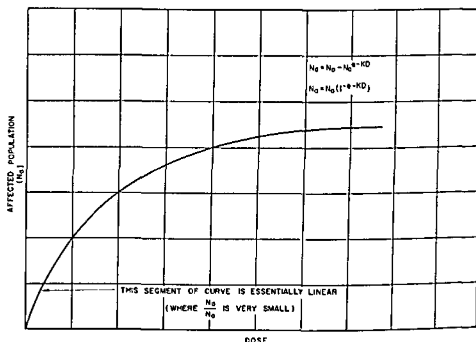
range. Secondly, it is interesting to note that a two-event curve fits these data essentially as well as a single event curve, suggesting that other types of curves could be used quite satisfactorily. You will note that if a two-event curve can be fitted, it means that there must be some type of threshold and a change in the rate of accumulation throughout the dose range might be present. Thirdly, note that the lowest dose is 25 roentgens Although lower doses have been studied in bacteria, plants, and unicellular organisms, this is the lowest dose that is available on complex organisms and, of course, is very far from the extremely small doses which are sometimes delivered to the gonads and are measured in a few milliroentgens.

Fourth, it is important to note that all of these studies are dependent upon establishing the natural mutation rate, which appears quite variable, and in the various studies show quite a wide range. Failure to properly establish this interferes seriously with establishing the exact character of the dose response curve

Fifth, it should be noted also in one experiment that Caspari and Stern found very little difference in the mutation rate of flies irradiated at 50 roentgens as compared with normal unirradiated flies The difference was considered by them to be *not* significant. This has been attacked by geneticists on the basis that these data were not satisfactory because of the unusually high natural mutation rate in their particular control flies.

Sixth, Bonnier and Luning have performed experiments on Drosophila and found that the *mutation* rate at low levels was considerably higher than that which *might* be expected on the basis of a linear curve proceeding directly to the origin.

Seventh, it should be noted also that the mutations which are studied in these experiments *are generally* known as point mutations – that is, there is no anatomical chromosomal alteration It has been established that the production of mutations by chromosomal aberrations is some type of multiple event function and is known to be clearly *non-linear* and may be represented by some type of power curve *It is interesting* that in examining the data on mutations, these mutants which appear to be the result of chromosomal effects *need to* be eliminated and there-




Having discussed the dose response curve in this way, I would like to proceed to the direct examination of some of the data which is available

First, let us consider mutations in which there are extensive quantitative data. The data which are available on a relatively complicated organism is that of Drosophila Figures are *available at several levels and down to relatively low doses* Typical material is that published by Curt Stern and his co-workers. In an analysis of these data it has been postulated that the curve appears to be linear through a fairly large range and appears to proceed directly to the origin It has been proposed, therefore, that this is evidence in favor of linearity and therefore is a single event function, and therefore indicates that the doses are cumulative and non-threshold. It should be pointed out, however, that there are *several points which deserve serious discussion* First of all, if one plots Curt Stern's data so that the curve assumes $N = N_o e^{-KD}$ form, only 8% of the total range is presented In other words, 92% of the organisms were unaffected for the lethal mutations which were observed This appears to be a narrow

very significant test and supports the concept of a cumulative non-threshold type of curve. However, I am very much intrigued by what Dr. Russell has reported today. He indicates that when 600 roentgens are delivered at once and then 600 roentgens delivered by fractionation or reduced intensity that the mutations are statistically fewer. This, to me, is a very important item, and in effect means that the test of linearity has not been met in mice. This could mean that there might be some threshold, or differing rates of accumulation with differing doses. I am sure that geneticists will wish to examine this closely. (Incidentally, I would like to point out here that I am not a geneticist and have examined this type of information as a radiologist and radiation biologist primarily to become informed on this important aspect of radiobiological effects.)

Still another test of linearity of the dose response curve can be made when varying types of ionization are used, so that the density of the ionizing events per unit volume is widely divergent. It has been postulated on a theoretical basis that appears quite sound that the more densely ionizing the radiation, the smaller the effect per unit of ionization. When the ionizations are densely packed, a single structure such as a gene or other target may be traversed by an ionization more than once. The subsequent ionizations only contribute to the dose but produce no added effect if only one ionization is necessary. It seems paradoxical that Muller quotes work by Ives *et al.* and by Mickey and Muller, in which radiation known to have a high density of ionization seems more effective in producing point mutations. I consider that there needs to be further resolution of this in order to satisfy the single hit concept.

Some other points of conflict have to do with the fact that when biological material is irradiated at various temperatures and varying oxygen pressure, the number of mutations vary. It has been reported variously that increase in temperature increases the number of mutants, and other data have indicated no differences in temperature. Temperature effects and oxygen effects might be important since there might be some indication as to whether a direct or indirect effect occurs.

fore the data for point mutations has actually been modified by the deletion of that number of mutants which have been estimated to be due to chromosomal aberrations.

One of the questions that is important to ask is whether there is any biological material that appears to respond in non-linear fashion to ionizing radiation. In searching through the literature, it appears that the spores of Actinomyces worked on by Kellner and by Newcome indicate that there is non-linearity with response to the radiation. Although these are presumably point mutations, it has been suggested that these may actually be chromosomal breaks, thus accounting for the non-linear character of the dose response curve.

It is also interesting to note that mutations as a result of ultraviolet radiation are uniformly non-linear. The exact significance of this is not clear, but in the radiation of biological tissue, some of the energy transfer should conceivably be in the form of excitation Since ultraviolet radiation may only excite, it appears that excitation produces some type of non-linear curve, and it is conceivable, therefore, that some fraction of the energy transfer of ionizing radiation may be a non-linear function.

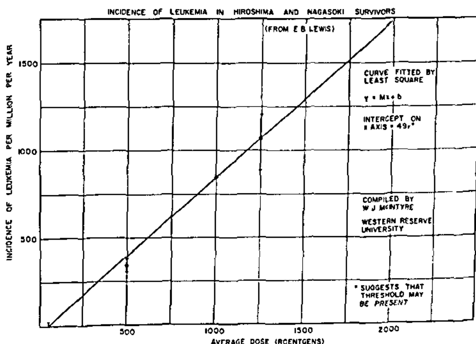
It is also of interest to examine possible tests of the linear curve — that is, testing of the curve by various manipulations may indicate whether this is indeed a single event function and therefore linear, or semi-logarithmic and therefore likely to be non-threshold and cumulative. A semi-logarithmic curve has in it some inherent built-in statements. In a single event function in which one event is independent of the other, fractionation of the dose should make no difference The density of the ionizing radiation should have certain types of effects and the character of the response should not be altered by extraneous occurrences One of the pieces of information which is strongly in favor of a single event or semi-logarithmic function is the fact that radiation has been given over a wide range of intensities and in widely fractionated doses. It appears that in the older literature, primarily on Drosophila, and partially accumulated by Lea in "The Action of Radiation on Living Cells" that fractionation and wide ranges of intensity give essentially the same response. This is a

level of leukemia must be known in order to establish the base line. The data that are used indicate that a lower naturally occurring incidence of leukemia was present for the Japanese — lower than is generally attributed to American and European populations It has been suggested that incomplete diagnostic methods may contribute to this. If the incidence of leukemia in the Japanese should actually prove to be higher than the level used in these studies, the character of the curve would be considerably altered and would tend to be in favor of the concept that a threshold might exist Additional information which is interesting in this respect is that in animals, fractionation of the dose appears to produce a lower incidence of leukemia If this were truly a single event function the incidence should be the same whether the dose is given at once or by fractionation.

Additional studies which might appear to support the thesis that leukemia is produced by low levels of radiation is that reported by Stewart in the *Lancet* This is a study which is retrospective in character and is designed to determine whether leukemic children received more radiation in utero than non-leukemic children The radiation was delivered to the mother and the fetus during pregnancy This is a preliminary study — in my opinion at best provocative and not conclusive The objections to the study are these (1) it is in the most part in the form of a questionnaire, and (2) it is not a blind study since the examiner knows which are the mothers of leukemic children and which are the mothers of non-leukemic children. The effects attributable to radiation must necessarily be very small from examination of the data. I do not recall the figures exactly, but about 500 mothers of leukemic and non-leukemic children were compared (in a contemplated study of 1500) In the mothers of leukemic children about 80 received abdominal x-rays of one type or another In the non leukemic group, about 40 mothers received x-rays It must be clear that 420 mothers did not receive radiation and the leukemia in these children must be attributed to some other cause Conversely, 40 of the non-leukemic children received radiation, which is not an inconsiderable percentage, and yet these produced no leukemia Although the differences

Because of the proposals in the case of mutations that this might be a single event function, certain somatic changes have been investigated from the point of view of the possibility of establishing these as single event functions as well. You are all familiar, I am sure, with the work by E. B. Lewis which was published in SCIENCE in which he tries to establish that the incidence of leukemia in Hiroshima and Nagasaki was essentially a linear sort of curve, proceeding to zero, and therefore postulating that there is no threshold for the production of leukemia and that the doses are cumulative no matter how they are fractionated or no matter how low the intensity It is difficult with the limitation of time to go into this completely, but may I report simply that the data as taken from his publication and handled by the method of least squares intercepts the axis at a considerable dis-

FIG 2




tance from the origin. (See Figure 2). This suggests that some type of non-linear curve would fit the data better. It is also interesting to note that in order to establish such a curve, the natural

ably this will not be possible until the exact mechanism of the production of biological effects by radiation is known. It will eventually be necessary to weigh the benefits of radiation against its risks. To do this effectively, both will have to be assessed very carefully.

*Dr. Russell:* May I ask a question? When you were discussing this 115 and 075, are these two gamma ray experiments?

*Dr. Friedell.* Yes, there are two gamma ray experiments.

*Dr. Russell.* X-ray experiment is, I think, higher.

*Dr. Friedell.* I'll get you the dope, but one may have been gamma and one may have been x-ray. I am not sure.

*Dr. Russell.* You did two gamma experiments, both at 50 r and then compared these with an acute experiment?

*Dr. Friedell.* Yes.

*Dr. Russell:* The first gamma experiment was by Caspari and Stern, which showed no significant difference between the irradiated and the controls. However, the control rate was unusually high.

*Dr. Friedell.* That's right.

*Dr. Russell:* And they invoke this as a possible explanation for the absence of a difference. And the second one gave a significant difference at the 3% level as I remember.

*Dr. Friedell.* That's right. That was Uphoff and Stern. I am using exactly the same data to show that a couple of things that they didn't compare really showed a difference. In other words, 24 hour exposure at 50 r, 21 days exposure at 52.5 r both having in essence age sperm, gave them these results which are statistically different.

*Dr. Russell:* Yes. So these were both gamma ray then. That's what I wanted to know.

*Dr. Crow:* The questions Dr. Friedell mentioned are discussed regularly by geneticists, and nobody regards them as finally and conclusively settled. Almost all studies have shown a strict proportionality between increased mutation production and dose, though there are some exceptions. The unusual rate in the controls may explain the Stern and Caspari results.

The problem in man is what happens at very low doses, and

in the two groups are statistically significant, the interpretation will, in my opinion, be elusive until much further work is done. It is clear that if radiation contributes to the increased incidence of leukemia in the fetus, it is in combination with some other causes and these are far greater than the contribution by the radiation itself.

The question of reduced longevity falls into exactly the same category. The data on humans are essentially nonexistent and practically all data are based on animals. It should be emphasized again that in order to conclude that small doses of radiation are cumulative, that a definite single event type of curve must be established. I believe that the evidence here is at best presumptive in animals, and certainly not conclusive. The only data that comes at once to mind on humans was published by Shields Warren in the Journal of the A.M.A. This purported to show that there was a decrease in longevity of radiologists as compared to other comparable specialists. It is very interesting to note that E. B. Lewis in his article in SCIENCE used another type of statistical analysis on these same data and concluded that the differences were not significant and might be expected statistically.

Before I conclude, I wish not to leave any improper impression I am certainly in favor of using radiation in the most careful and sanitary fashion. I believe certainly that precautions against the excessive use of radiation are necessary, and I am not in any way opposing the idea that radiation produces serious biological effects. However, a very important aspect of the problem is determining whether the biological effects are non-threshold and completely cumulative. I am raising the question *that the data for the cumulative non-threshold concept is not conclusive*, that many aspects are equivocal, and there is a strong possibility that a non-linear dose response curve might eventually be established, particularly for somatic effects As I have repeatedly stated, a non-linear dose response curve would almost certainly mean that there would be some type of threshold and incomplete accumulation of the effects

In the final analysis it will be essential to fully establish the dose response curve for various types of biological effects Prob-

# POPULATION ASPECTS:

## Assessing the Impact on Future Generations of an Increased Mutation Rate; How Damage Might Be Distributed in Time; and the Extent of Uncertainty of the Problem*

By

JAMES F. CROW, Ph.D.
*Professor of Genetics*
*University of Wisconsin*
*Madison, Wisconsin*

I think a radiologist might be tempted to ask a geneticist why, in view of the fact that the production of mutations by x rays has been known for three decades, many geneticists have only recently begun to express their concern about possible hazards from radiation in medical practice. I think the answer is more than just the growth of public interest in radiation following the discovery of nuclear energy and fallout.

For one thing, some geneticists, notably H. J. Muller, have not waited until recently. At the time of his great discovery in 1927 Muller called attention to this possible implication of his findings.

However, there are two scientific results that have caused geneticists to revise upward their previous quantitative notions about possible hazards. One of these has already been mentioned — Dr. Russell's finding that the mutation rate in the mouse is some 15 times as high as that in Drosophila, which previously had been the sole basis for quantitative extrapolation to man.

The second finding is that most "recessive" mutations that have been studied carefully turn out not to be completely recessive, but to have appreciable effects in a single dose. If two doses of a mutant gene are required to produce the effect, any harmful effect will be delayed until by coincidence or consanguineous

I have one reservation about Dr. Friedell's emphasis on studies of intensity variation and fractionation at high doses. I suspect that in many circumstances we are dealing with a mixture of single and multiple hit effects. If only high doses are studied, multiple hit effects may predominate and intensity and fractionation effects will be observed, whereas at sufficiently low doses single hit effects would become predominant. I think that linearity at high doses generally implies linearity at low doses as well, but curvilinearity at high doses does not preclude linearity at low doses. I think that low dose studies of somatic effects, despite their great expense, are very much in order.

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The second finding is that most "recessive" mutations that have been studied carefully turn out not to be completely recessive, but to have appreciable effects in a single dose. If two doses of a mutant gene are required to produce the effect, any harmful effect will be delayed until by coincidence or consanguineous

marriage two corresponding mutant genes occur in the same person. The average delay might be hundreds or thousands of generations. However, if there are appreciable effects in single dose those would begin in the immediate progeny and the total effect would be spread over dozens rather than hundreds or thousands of generations. These two findings suggest that human effects are likely to be greater and to occur sooner than previous estimates had indicated.

Finally there is a somewhat changed opinion about somatic effects. There is now much wider acceptance of the possibility that leukemia and other malignancies at least in some cases may be due to somatic mutation or some other process that is kinetically equivalent. The heritability and transmissibility by single cells of experimental tumors suggests the possibility of etiology by way of some event in a single cell The analyses by Court-Brown and Doll (1) and by Lewis (2) of leukemia in irradiated populations suggest the possibility that there may be no threshold and that low doses of radiation may produce malignancies

For all these reasons I believe that the current concern is justified and that it is quite proper that a new look be given to possible radiation hazards in medical practice I am therefore appreciative of the interest in the question that this symposium indicates.

## A SHORT SUMMARY OF THE ACCEPTED PRICIPLES OF RADIATION MUTAGENESIS

During the past three years the genetic effects of radiations have been reviewed in so many papers and committee reports that only a heavily shielded person could avoid encountering at least one of these missives (3-5) I'll confine myself to a quick

[1]Court-Brown, W M and R Doll 1957 Leukemia and aplastic anaemia in patients irradiated for ankylosing spondylitis *Medical Research Council Special Report No 295*, pp 1 135 Her Majesty's Stationery Office

[2]Lewis, E B 1957 Leukemia and ionizing radiation *Science, 125* 965 972

[3]The Biological Effects of Atomic Radiations *Summary Reports* 1956 National Academy of Sciences—National Research Council, Washington pp 1 31

summary of current genetic opinions. The main points are these:

1. Mutant genes, whether spontaneous or radiation induced, are generally just as stable as the original genes from which they were derived; that is, there is ordinarily no "repair" of a mutant gene. Therefore, we conclude that a mutant gene persists in the population until it is eliminated by the premature death or failure to reproduce of an individual carrying it. Mutant genes, may, of course, be eliminated by chance, but they are exactly balanced by those that multiply by chance. Also there may be reverse mutation, but this is too rare to require consideration here

2. The weight of evidence indicates that the number of mutations produced is largely independent of the intensity or spacing of the radiation, as long as the total dose delivered to the pre-reproductive gonads is constant. For example, 100 r given in one minute, or in two widely separated doses, or at a very slow rate over a long period of time have the same effect. The inference drawn from this is that ionizations from independent ionizing particles do not ordinarily interact. Most of the evidence comes from irradiated Drosophila sperm, and more data from other organisms and other stages are needed.

3. The number of mutations is linearly proportional to the dose in roentgens (or better, rads). This has been demonstrated in Drosophila for doses as low as 25 r and to a lesser extent in many other experimental animals and plants. Unfortunately, the data don't extend to as low doses as those likely to be encountered by the human population, and it is an important question whether extrapolation to lower doses is *justified*. Geneticists are convinced that the linearity persists down to zero dose with no threshold, for several reasons: the line correctly predicts the spontaneous mutation rate when extrapolated back to zero dose; the lack of intensity or spacing effects mentioned above argues for the independence of each ionizing particle as a mutagenic agent.

[1] *The Hazards to Man of Nuclear and Allied Radiations* 1956 Medical Research Council. Her Majesty's Stationers Office

[2] *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation* 1958 *General Assembly Official Records* Thirteenth Session, Supplement No 17 (A/3838)

at very low doses spread over a long time there are hardly ever two or more ionizing particles simultaneously near together so there is no obvious physical basis for a non-linear effect. For these and other reasons, geneticists are convinced of the linearity at low doses (5).

I should mention that I have ignored numerous complicating factors. For example, spermatids in Drosophila are more mutable than spermatogonial cells, but spermatid radiation is a very small (and often preventable) part of human exposure. Also those hereditary changes that depend on gross chromosome changes do not follow the linearity rule given here, but these are rare at the low doses being considered. I think none of the various complications are such as to alter appreciably the general conclusion of linearity of genetic effects at low doses.

## NATURE OF MUTATIONAL EFFECTS

We are all familiar with various inherited diseases that occur by mutation — e.g., achrondroplasia, hemophilia, retinoblastoma, agammaglobulinemia. Undoubtedly part of the effect of an increased mutation rate would be a somewhat increased frequency of such conditions. But there is good reason to think that most of the genetic harm from an increased mutation rate would be of a less obvious sort. Evidence for this comes primarily from two sources. One is Drosophila studies. These have shown that mutations that cause death (lethal mutations) are much more frequent than those causing an obvious visible effect. But still more frequent than those that, while not causing certain death, increase the probability of death by a statistically detectable amount. Such mutations appear to cause minor impairments in the body function, such that the fly is more likely to succumb to the usual vicissitudes of life than if it did not carry the mutant gene (7).

[6]Muller, H. J. 1955. How radiation changes the genetic constitution. *Bull. Atomic Sc.*, *11* 329-339.

[7]Muller, H. J. 1950. Our load of mutations. *Am. J. Human Genet.* 2 111-176.

There is also indirect evidence from human sources. There is good reason to think that genetic weaknesses that owe their origin to mutation are uniquely revealed by inbreeding. Thus we can get an idea of the nature of mutational effects by examining the children of cousin marriages and other consanguineous unions (8). There is so far a dearth of really satisfactory quantitative data on this subject, but from what data are available the conclusion is quite clear: children of consanguineous marriages have an appreciably higher death and morbidity rate than their outbred contemporaries. The causes of death are the usual ones encountered in children of non-consanguineous marriages; relatively rarely are they due to recognized genetic diseases.

From this evidence from Drosophila and man, and from our belief that most genes exert their major effect on the population in single dose (7), it would follow that a large share of the genetic damage to the population would be a general weakening due to various kinds of minor impairments, leading to increased death and morbidity rates rather than to specific recognizable genetic diseases.

The fact that much of the genetic damage is of this form, where it would not ordinarily be recognized as such, makes it particularly difficult to assess. Some geneticists have preferred to ignore this as being too intangible to deal with, and have concentrated on specific genetic diseases where there are more precise predictions of the social and medical consequences. I must say that to me this seems somewhat like measuring only that part of an iceberg that appears above the surface of the water.

We cannot take the sanguine view that if most mutations are mild, they are therefore less important. If a mutant gene causes its bearer a great deal of harm it is likely to interfere with his survival and reproduction. If he doesn't survive or doesn't reproduce the mutant gene is eliminated. In general the less harm a mutant causes, the longer it persists in the population. Therefore if its effect on each individual is less it will affect a corre-

[8] Morton, N. E., J. F. Crow and H. J. Muller. 1956. An estimate of the mutational damage from data on consanguineous marriages. *Proc. Nat. Acad. Sc.* 42: 855-86[illegible]

spondingly larger number and the overall effect on the population may be just as great or greater.

There is considerable uncertainty about the effect of an increased mutation rate on genes of small effect, genes whose individual effects cannot be noted but which are thought collectively to influence quantitative traits such as height and weight. To the extent (now unknown) that the present frequencies of such factors are determined by balance between selective forces rather than by mutation, an increased mutation rate will not cause a proportional change in their effect on the population. However, the genes studied in Drosophila and in the mouse, and on which all the quantitative extrapolations to man have been made are not of this kind.

## DISTRIBUTION OF MUTATIONAL EFFECTS IN TIME

As mentioned before, it used to be thought that most mutant genes were completely recessive. In this case a mutant gene would remain in the population causing no effect until, because of a consanguineous marriage or by meeting a similar mutant of independent origin, two mutants occurred in the same individual. On the average this would require hundreds or thousands of generations with present levels of inbreeding.

However, there is now abundant evidence that mutant genes that have a lethal effect when in a double dose cause appreciable damage in single dose. In Drosophila a "recessive" lethal causes a five percent or greater decrease in the survival rate (7, 9)*. Presumably there is the same absence of complete recessiveness in genes whose homozygous effects are less than lethal, but this point has not been explicitly tested. However there is indirect supporting evidence for this conclusion.

If a number of new mutations were to occur now, the mutant genes would persist in future generations in inverse ratio to the extent to which they affected survival and fertility. I find it con-

*Stern, C., G. Carson, M. Kinst, E. Novitski and D. Uphoff. 1952. The viability of heterozygotes for lethals. *Genetics*, 37: 413-419.

venient to express the time over which the population is affected in terms of the "half damage time". This is the time by which half the mutants have been eliminated and therefore half the damage has been done. One can only guess at what this time is in man; from Drosophila data one would estimate it as from 10 to 50 generations (10, 11). So an increased mutation rate now would have effects spreading over thousands of years, diminishing gradually over this time.

## QUANTITATIVE ESTIMATES

If the mutation rate were to be permanently increased by a certain fraction, say 10 percent, eventually the incidence of mutationally caused disease and death would increase by this same fraction. If we assume for convenience that the population started at an equilibrium where new mutants were being eliminated at the same rate that they were arising by mutation, then it would require many generations for the new mutation rate to be fully manifested in an increase in morbidity and death. The approach is asymptotic so it is convenient to speak of the time in which the population moves 50 percent of the way to the new equilibrium. As before, this is probably 10 to 50 generations. The general result then, of a permanent increase in the *mutation rate* is a slow rise in the frequency of all mutationally caused conditions until they have increased by the same fraction as the mutation rate.

If we wish *to* say anything quantitative we have to rely on data from mice, there being no quantitatively reliable data on man. If we compare the rate of occurrence of x-ray induced mutations in mice with spontaneous mutation rates in man, we find that some 30-50 rad are required to cause in mice a rate equal to the spontaneous rate in man (3, 4, 5, 10). Thus a 30-50 rad

[a]Crow, J. F. 1956. The estimation of spontaneous and radiation induced mutation rates in man. *Eugenics Quart.* 3:201-208.

[b]Crow, J. F. 1957. Possible consequences of an increased mutation rate. *Eugenics Quart.* 4:67-80.

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a later age is a major tragedy. How do we compare physical with mental disease? How many persons whose health is mildly impaired equals one seriously diseased? Furthermore, how do we compare disease this generation with genetic impairment later when medical progress in care and alleviation will have changed the nature of the disease?

Yet it is only by attempting such measurements that any rational procedure for decision making can be evolved. For in principle each decision involving radiation must be made by balancing the risk to the patient of not carrying out the radiation against the risk to his descendants (or to his later health from somatic effects) if the radiation is given.

The problem of measuring future damage is complicated by the fact that our environment is changing so rapidly. In general these changes are such as to mitigate the effects of the mutations. But since reducing the amount of suffering and death due to a disease usually causes an increase in the chance of reproduction, correspondingly more persons will be affected by the mutation. An environmental improvement is thus more like a postponement than an obliteration of genetic damage. From this standpoint the most useful medical or environmental advance is one that reduces suffering and unhappiness more than it increases fertility

Thus the problem of an increased mutation rate becomes a part of an overall problem of the relation between genes and a rapidly changing environment.

*Dr. Evans*· Is there any specific question on interpretation or understanding that you would like to ask?

*Dr Pitkey* I would like to have some idea from the geneticists on the effect on the population of the deaths from automobile accidents as compared to this overall radiation effect

*Dr Crow* I don't have the figures in mind, but certainly if you consider only gross abnormality the number of deaths from automobiles is considerably larger.

*Dr Friedell* I made a calculation that if you ride in an automobile the same amount from now until you die naturally, the chance will be one in a hundred. It's easy to make the cal-

dose per generation might be expected to double the human mutation rate

If the amount of radiation from medical treatment is of the same order as background radiation (say, 3 rad) it may be estimated to be responsible for increasing the mutation rate by about 10 percent, and thus to cause, if continued, an eventual 10 percent increase in genetic impairment.

It is easier to say that the increase is a certain percent of something than it is to say what that something is According to the National Academy of Sciences Report (3, see also 5), about 2 percent of children born have or will have a serious genetic impairment. A 10 percent increase would add 0.2 percent to this. Relative to other hazards in life, this is small. At the same time in a large population the absolute increase would be great. Furthermore, I have included only the simply inherited tangible effects. If what I have been saying is correct, the overall impact of individually small mutants would be much larger I have given some rather uncertain estimates of this elsewhere (11).

## UNCERTAINTIES

One of the most serious defects in our present knowledge is the absence of quantitative human data One could extrapolate from data on mice with more confidence if other mammals had also been studied. The only information to be drawn from the Hiroshima and Nagasaki populations is that human mutation rates are not grossly higher than those of mice If, for example, man were as much more mutable than mice as mice are than Drosophila, the effect should have shown up as significant differences in the data

Even if we knew the radiation induced mutation rate with precision, the assessment of the impact of an increased rate on the population poses almost insuperable problems What we need is some overall measure of the social burden — the effect on health and happiness — of mutation A mutant that causes an early embryonic death may be of little consequence, a death at

a later age is a major tragedy. How do we compare physical with mental disease? How many persons whose health is mildly impaired equals one seriously diseased? Furthermore, how do we compare disease this generation with genetic impairment later when medical progress in care and alleviation will have changed the nature of the disease?

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*Dr Friedell* I made a calculation that if you ride in an automobile the same amount from now until you die naturally, the chance will be one in a

culation. There are 40,000 deaths from automobile accidents a year, out of 160 million people, multiplied by the number of years you are likely to drive, this will tell you the chance. It's pretty high — 1 in 100 of being killed in your lifetime by an automobile.

*Dr. Pitkey*: One can express that another way — that the average life shortening by automobiles is of the order of one year.

*Dr. Crow*: Such comparisons are useful in giving us perspective. However, I think each health hazard ought to be regarded not so much as to whether it is bigger or smaller than something else but as to whether it is preventable or not. The main reason for really discussing radiation damage here is the hope or the possibility that whatever this amount is, even though small, it might possibly be reduced. And I would say the same thing about automobile accidents; they can and should be reduced

*Dr. Brues*: This has perhaps an historical basis. Sometime ago all of these things were judged on the basis of how much was permissible. Then when it became clear that we didn't have the data to determine what was permissible in some cases, we found that it was necessary to look at what people were willing to put up with for certain gains. The philosophy is a questionable one, but this is one way at least of seeing what people are willing to put up with when they have a choice

*Dr. Crow*: If you take the best guess I can make from mouse data, you might say that a person who receives 20 r to the gonads would have about one chance in 20 of transmitting mutations that would cause a substantial effect in some descendant. As a very crude test, you might ask yourself, before giving such a dose, whether the good that you're doing for this person will more than compensate for a risk of 1 in 20. I want to emphasize that my estimate of 1 in 20 may be grossly wrong, but it serves as an illustration of the kind of approach one could consider.

# DISCUSSION OF LEUKEMIA AND RADIATION

By

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In regard to the patient who objected to having his chest film, it is possible to point out certain things. The best guess is that under usual conditions, the gonadal dose is about .5 mr. from a routine chest film. This is about the additional dose which you would get on an airplane trip overnight to the West Coast or to Europe at 21,000 feet altitude. Since this was an x-ray machine, the man was disturbed because he had not considered it in such a context. The dose to his chest is perhaps 100 mr. Taking the worst possible assumption as to the hazard of leukemia or cancer with this dose being about $10^{-7}$ per year or so, it is possible to point out to him that at his age there is about a $10^{-4}$ chance of his developing lung cancer. We may assume that surgery offers about a 20% chance of curing one discovered early by routine radiography. So there is a factor of something *more than 100* between any conceivable risk for the man, and what benefit would possibly be gained, leaving out the question of tuberculosis and other lesions which may vary from place to place.

We have to look at these things intelligently. The whole question has developed certain *psychiatric aspects* which should concern all of us. We should think carefully about these things. We can perhaps legitimately assume that radiation is in the main a harmful thing. Much of the additional concern is due to the fact that many persons who are terrified by the holocaust that might occur if we have nuclear or thermonuclear war, will not admit this to themselves. They *transfer* their anxiety to simpler things and, I think, particularly to leukemia. We have been

told, on inadequate evidence, that the hazard of leukemia following radiation is a straight-line function of radiation dose. This is based on a simple somatic mutation theory, assuming that a simple point mutation in a cell causes a tumor. We may recall, however, that in the human bone marrow, there are about 10-11 proliferating myloid cells. Assume that most of those might be cells in which a leukemia could originate. If the leukemia rate per r per year is estimated at about $10^{-6}$, or one in a million, and if this is spread over ten years, which is based on the best evidence, we come out with a cell mutation rate producing leukemia around $10^{-16}$. This is an extremely low value and it forces one to conclude that there must be something besides one mutation in one cell that causes leukemia. Maybe it is two or three mutations in the same or adjacent cells, in which case, you would not get a linear relation It might possibly be a combination of *things that radiation has nothing to do with; we don't know.* Now, if we consider the mouse (who has a comparable leukemia rate) he does not live as long and does not have as many cells. His mutation rate has to be different from that of man by a factor of 10,000 or 100,000 If there is that much difference between the mutation rate of the somatic cells of a mouse and of a human being, somebody should look into this rather basic question If this is not the case, then this means that the situation is a little more complicated than that of a single point mutation.

Court Brown and Doll have made a careful study of persons who received spinal irradiation for spondylitis, and infer that there is a linear relationship between the amount of radiation in the spinal marrow and the number of leukemias The linear curve was obtained only by the device of cutting out a certain category of cases which happened to include about 80% of the cases which were in the highest dosage category Lacking this (I think) illegitimate selection of cases, we find that the leukemia incidence departs from a straight line and suggests a very small, or no response, at low doses

We have also examined the number of leukemias which were observed in the various zones at Hiroshima At the time these data were first published, it seemed as though they made a

straight line with dose, but they no longer do with further data now available. All that we can say at present is that doses above 100 r are leukemogenic.

About a year ago, the geneticist, Dr. E. B. Lewis, furthered the straight-line theory by using the data discussed above. If we repeat his data on a logarithmic graph, we find that a better fit is obtained if we assume that the leukemia hazard follows the square of the dose, or if there is a true threshold, at around 70 r.

Probably the most striking data are those on the incidence of mouse leukemia following various doses of gamma rays and neutrons The two behave rather similarly, judged by Upton and Furth's study. What one sees here essentially is an increase, particularly when one gets up to about 120 r exposure, and some effect has been suggested as low as 12 r. The data are not sufficient in scope. This, I think, is true of all data on animals that have been obtained so far to demonstrate whether or not there is a linear relation between myloid leukemia and radiation exposure It is very definite that there is not such a relation between lymphatic tumors and irradiation, as I think is well known

Perhaps the most disturbing data are based on a survey by Alice Stewart. Similar findings have been obtained in a Louisiana study These are studies of childhood leukemics whose histories have been traced. They found that if a child has *leukemia*, there was a greater probability that he was x-rayed *in utero*. While the excess is about two times, the actual increase in Stewart's series amounts to about 18 cases There is also a similar excess in the case of cancers occurring below the age of 10 This could be a serious matter *This* has been criticized in various respects One objection is to the effect that pelvimetry is sometimes done on the basis of some medical indication and that this indication might in some way represent a particular state of heath

The other thing to mention is that one ought to look at as many possible potential causes of childhood leukemia as possible and not limit consideration to radiation A study done by the Public Health Service, using Dr. Sidney Farber's clinic seems to show that children of allergic mothers, who incidentally had been on

antihistiminic drugs, showed a similar relationship. They turned up more frequently in the motherhood of the leukemic children than in the motherhood of the controls. I would only mention for the benefit to the radiologists who are here that studies of this general nature are tremendously important. They must be done quite judiciously, because it is very easy to embark upon a followup of a series of cases where it can be demonstrated that a positive answer cannot be obtained. So far, the retrospective studies have been very difficult to evaluate. For instance, when one looks at a clinic full of children and attempts to trace these things back and tries to draw a correlation between them, a very small population of leukemics will represent a very large total population Certainly there are other leukemogenic agents than radiation. The incidence of leukemia when corrected for probable improvements in diagnosis has certainly more than doubled in the last twenty years in this country during a period when I am sure that the total radiological exposure of individuals has gone up somewhat less than that. Besides, we know of other leukemogenic factors

*Dr. Evans*: The discussion on the morning session is now open to the floor

*Dr. Lodwick*: Just one question. What genes are absent on the Y chromosome of the male?

*Dr. Herskowitz*: On the fruit fly, they are all absent except for a few fertility genes, and in humans there is a section of genes on the X chromosome not present on the Y

*Dr Crow*: In the human you realize we don't know too much There are known to be several on the X, but we don't know whether there are any on the Y or not

*Dr Friedell* I would like to ask Dr Crow a question X-rays produce deleterious mutants which are introduced into the entire gene pool One of the ways of adding to the deleterious genes is by changing the rigors of selection It is conceivable that medical science is adding to our deleterious genes without completely compensating for them Would you elaborate on some aspect of this a bit?

*Dr. Crow*: I have one thing I want to say before I start on

this discussion If we were treating the question of the origin of leukemia strictly as a scientific question, everybody would say that the evidence isn't in yet. We don't know whether there is a linear effect on low doses, so therefore, we don't say anything about it. There is no evidence that is crucial either way. We have the kind of evidence that Dr. Brues has reviewed, most of which is relevant for high doses, but less certain for low. We have the kind of evidence which Lewis has put together, which is inconclusive though strongly suggestive. Under those circumstances, I think an agnostic attitude is all that we can take. Until the evidence is clear, I think there is merit in basing our calculations and practical decisions on the more pessimistic assumption of no threshold I have the same remark about Alice Stewart's data. It is strongly suggestive, but I would certainly agree with Dr. Friedell that retrospective studies can never conclusively answer cause and effect relations and that we must try to get information from other sources

Regarding this other question, I grossly oversimplified this problem, though I hope not to the extent of being misleading But I think from the standpoint of the medical man and the eugenecist that the way to look at it is this. I suppose we have a mutation that occurs at a rate X and it causes death. That means in every generation there are X deaths due to this cause. Now suppose that medical advance takes place in *such a way that* this particular mutation has only a 50% probability of causing death That means that this population is going to approach a state in which *there are* 2X of these genes in the population every generation Since each of them now causes *only half* a death, on the average, there will still be X deaths. Now I think the important question to ask is whether the *amount* of suffering to the human population from 2X mutations in the new environment is less or more than it was *from* X mutations in the old environment To restate this in other words, I think that a medical advance that decreases suffering more than it increases fertility is a good medical advance A medical advance that increases fertility more than it decreases suffering is, eugenically speaking, a bad medical advance

*Dr. Friedell:* I don't want to prolong this conversation. The only reason I brought it up is that it is conceivable that some day you might want to measure the introduction of new genes that are deleterious. Let us assume essentially they are all deleterious, by x-rays as compared to the kind of suffering, if this condition occurs, by ameliorating the rigors of selection, which is what you are really doing with medical advance. I would like to have the geneticists do that rather than me do it.

*Dr. Crow:* Well, the geneticists ought to be doing it. I for one have spent a lot of time thinking about it. I don't think it is very apparent from what I have said now, but the time was spent. The other thing I want to say is that I have more or less assumed in what I have said thus far that the economic status is well enough that we can afford to contribute to every generation a larger fraction of our time to taking care of genetic weaknesses in the other person. That is, if we should ever reach a state where we can't afford to have as many doctors as we used to have or we can't afford to have as many blood banks or whatever else it takes, then one has to consider the genetic problem over again. I think that inter-relates economics, medicine, eugenics and everything into one hopelessly complex problem.

*Dr Paul Hodges* In diseases where the incidence is as low as in leukemia, it is easy to be trapped into a statistical error. Some years ago we did pelvimetries on a thousand consecutive pregnant women at the Chicago Lying-In Hospital and I, like many of my students and colleagues, made the statistically foolish mistake of assuming that it would be profitable to examine these mothers and their babies for leukemia and neoplasm One of my extremely capable statistician friends saved me from this error by pointing out that even if our pelvimetries had doubled the normal incidence of leukemia (normal, 6 per hundred thousand) we could not hope to get statistically valid information from an examination of a thousand patients In situations such as this, investigations have to be based on statistical analyses of whole populations

*Dr. Crow:* I want to make two other remarks exactly confirming what Dr Friedell has said Maybe everyone here is

familiar with Dr. Shields Warren's study in which he suggested that radiologists lived five years shorter on the average than other medical specialists. This is a retrospective study, it's done by gathering death rates from the obituaries published in reputable journals But it has a very obvious statistical fallacy, the fallacy simply being that radiology is a comparatively young profession and that there aren't as many radiologists to examine. It is almost as if you measured the age of death of all Princeton students You would conclude that Princeton students died at an extremely young age because those who die while they are students are young. There are other things about questionnaires. Mock and Lawrence ran a study of radiologists and I ran one at the same time Our two questionnaires differed in one conspicuous respect, and maybe some of you were among the guinea pigs that answered one or both of these. Mock and Lawrence's were done by taking the respondent into his confidence and telling him the purpose of the questionnaire and then getting the answers Mine was done by intentionally concealing the purpose of the questionnaire, at least until that person started to answer it There is a very conspicuous thing in Dr. Mock's data That is that the persons that he had to write back to the second time and who failed to answer it the first time have a higher miscarriage frequency than the persons who answered the first time. He never did get as many responses from the pathologist group as he did from the radiologist group It seems quite reasonable that had he been able to get as many pathologists to respond, and recognizing this bias in favor of those not responding if you had had some defect in the family, perhaps this difference would have disappeared

*Dr Brues* Might I add for the benefit of those who may still be worried about their life spans, that the British have now done a study on all British radiologists going back to 1898 or whenever they started.* They find, having done the eight corrections which Warren apparently did not do, that radiologists

*Brown, W. M. C. and Doll, R. Expectation of Life and Mortality from Cancer Among British Radiologists British Medical Journal, Vol 2 (July 26, 1958), pp 181 187

had a better survival than in some controlled series of doctors

*Dr. Scott:* In the February 8, 1958 issue of the J.A.M.A. is an article by Seltser and Sartwell on "Ionizing Radiation and Longevity of Physicians," which concludes, "that the average age of radiologists at death is younger than that of other physicians cannot be ascribed to their exposure to ionizing radiation since differences in age composition alone can account for the finding."

*Dr. Friedell:* I think Lewis pointed this out very well. In his one article, he made this particular analysis showing that statistically the difference that was found was to be expected.

*Dr. Evans:* I think everybody will agree that regardless of the amount of the problem, we certainly want to reduce radiation exposure to the gonads insofar as is feasible and this is going to be taken up by the clinicians as to how they can best do it

## AFTERNOON SESSION

## THE PROBLEM OF REDUCING RADIATION GENETIC EFFECTS IN THE MEDICAL USE OF X-RAYS

*Moderator: Wendell G. Scott, M.D.*

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# GROWTH OF DIAGNOSTIC RADIOLOGY AND MAGNITUDE OF PROBLEM

**WENDELL G. SCOTT, M.D.**
*Professor of Clinical Radiology*
*Washington University School of Medicine*
*St. Louis, Missouri*

Dr Scott: The afternoon session is devoted to the problem of reducing radiation genetic effects from the medical use of x rays

By way of introducing this subject, I would like to show a few slides to indicate the magnitude of our problem Diagnostic radiology has had a tremendous growth because of the great contributions it has brought to the health and well being of mankind This was not due to accidental or fortuitous circumstances It came about because it was and still is the means for lifting the cloak of uncertainty from diagnostic medicine Nearly every practicing physician either directly or indirectly utilizes the indispensable advantages offered by diagnostic radiology for the benefit of his patients The total number of radiologic examinations and the films consumed per year are in the millions (Table I)

TABLE I

ESTIMATED ANNUAL NUMBERS OF RADIOGRAPHIC EXAMINATIONS FILMS CONSUMED AND DIAGNOSTIC X-RAY MACHINES IN 1955

| | |
|---|---|
| [illegible] | [illegible]s |
| [illegible] | [illegible]ologists |
| [illegible] | [illegible] |
| [illegible] | [illegible]ipment |
| [illegible] | [illegible] 1955 |

Source Laughlin & Pullman (1)

[1]Laughlin J S, and Pullman I The Biological Effects of Atomic Radiation (Gonadal Dose From the Medical Use of X Rays—Preliminary Report) National Academy of Sciences Washington, D C, March, 1957

literature and *estimated* it to be 4 6 roentgens ± 3 in a preliminary Report that has not been officially released by the National Academy of Sciences. This figure is not a fact. It is a rough estimate based on data of varying reliability. The report in October, 1957 by the International Commission on Radiological Protection and on Units and Measurements (3) states that, "Enquiries up to the present have not revealed any records detailed enough to use for the proper assessment of the gonadal doses to the population." In a subsequent paper, Laughlin and associates (4) discuss the studies and surveys that are required for obtaining the necessary information to develop this figure. Until this can be done and an accurate estimate of the genetically significant gonad dose determined, we must be extremely cautious about accepting or formulating quantitative inferences from diagnostic x-ray prodecures

In the assessment of the possible deleterious effects arising from the medical and dental use of x-rays, it must be clearly understood that: (1) Only small doses of radiation are used in clinical examinations, and (2) the exposures are limited to local or segmental areas of the body as opposed to total body irradiation Many of those who emphasize the bad effects of diagnostic exposures do not distinguish between local and total body radiation The "roentgen" is the measure of exposure to each gram of tissue, and as Stone (2) points out, "1 roentgen to a toe is vastly different than 1 roentgen of total body exposure".

With these introductory remarks, we are ready to proceed with the problem of reducing radiation exposures in our clinical examinations The first paper is "A Trial Balance of the Results of Clinical Exposure to Ionizing Radiations," by Dr Theodore Eberhard

[2]Stone, R S Common Sense in Radiation Protection Applied to Clinical Practice American Journal of Roentgenology Radium Therapy and Nuclear Medicine, 78 993 999, December, 1957

[3]Exposure of Man to Ionizing Radiation Arising From Medical Procedures—An Enquiry Into Methods of Evaluation Report of the International Commission on Radiological Protection and International C[illegible]
Measurements Physics in [illegible]

[4]Laughlin J S Meurk[illegible]
Gonadal Doses in Routine [illegible]

Add to these figures the 5,000,000 radiographs and the 1,900,000 fluoroscopic examinations that are performed annually by the osteopaths, the chiropractors and the chiropodists and it becomes readily apparent that we are dealing with a big and an important problem

The observation that the number of physicians owning radiographic equipment has increased 50% from 1949 to 1955 is disturbing and probably reflects the introduction of health plans that permit the subscriber to have "free x-rays," a temptation that can be corrected by instituting a deductible type of health insurance.

To keep these figures in the proper perspective, remember that the great bulk of these procedures are made on sick people, on those seriously ill with an obvious short life expectancy, and on those over 30 years of age. Only a small percent of the total could be considered as unnecessary or needless exposure. Most physicians are careful about ordering radiographic examinations and do so only when the benefits will outweigh the possible harmful effects.

Similarly, we should not overlook that during the past 50 years simultaneously with the expansion of diagnostic radiology, the life expectancy increased from 49 2 to 68.07 years; the death ratio from tuberculosis dropped from 194 to 9.1 per 100,000; infant mortality fell from 99 9 to 26 4 per 1,000 live births; fetal deaths dropped from 23.9 to 17.1 per 1,000 live births, and, that American children today are said to be taller, healthier and have a lower death rate than before Stone (2), who assembled these statistics, points out that while radiology cannot lay claim to being the major reason for these great medical achievements, it played a very conspicuous part. His inference is that if radiations of this order contribute to the shortening of the life span and produce genetic damage, they are not yet evident.

It would be of great help in determining the extent of the genetic problem if we knew the average gonadal dose the population was now receiving from medical and dental sources and how it compares to natural background radiation. Laughlin and Pullman (1), March, 1957, attempted to do this by a survey of the

of x-rays and radium. Radiation induced carcinoma and anemia were recognized within a few years The leukemogenic effect and the genetic effects have been known for over a quarter of a century. The so-called law of Bergonie and Tribondeau that sensitivity to radiation is inversely proportional to the degree of differentiation was formulated over 50 years ago, largely on the basis of observations of the effect of radiation on embryos These truths we also hold to be self evident

What is not self-evident is the magnitude of the factors involved How much radiation is necessary to produce a given effect? What is the relation of the age of the individual to the dose necessary for any given effect? Are all end-results without threshold in their inception? To what extent are various somatic responses linear in relation to dose? What is the effect of the rate of administration upon the ultimate response? What is the range of the variability of response in any given group of humans? To what extent are radiation responses dependent upon co-factors in the genetic, hormonal, and environmental profile? To all of these questions and many more we must have factual answers, reliable within limited ranges or small orders of magnitude, before we can truly assess the individual and the aggregate hazards

This does not mean that we have no guide lines nor that our lack of precise knowledge justifies the indiscriminate and careless use of ionizing radiation We have impressive evidence of a linear relation of dose to genetic response from 25 r up, regardless of the rate of administration, and strongly suggestive evidence of linearity at much lower levels If our analysis of the mechanism of genetic effects is correct, there is no logical reason to expect anything but *complete* linearity without *threshold* for point effects At the same time, we do not know the relative probabilities of lethal mutations and merely damaging changes, nor what constitute significant genetic injuries as opposed to those of no consequence How fast can the human race breed out undesirable traits and what burden of these can the race tolerate? What is the relative importance of radiation induced mutations and those resulting from other noxious factors? Dr David Barr has

able that with prolonged non-radiologic studies, the anatomic and dynamic aspects of congenital cardiovascular malformations would have become sufficiently well known to establish an adequate base for the accurate diagnoses and intricate surgical repairs so common today, but it is certain that this development would have been delayed many years while many hundreds of children paid the supreme price for our ignorance. Only those of us who lived and worked on neurosurgical services before the full development of pneumoencephalography, ventriculography, and cerebral angiography know the heartaches and tragedies that went along with attempts at the clinical localization of brain tumors followed by futile mauling and probing of the brain in vain search for the lesion. Only too often we found at autopsy that we had been at the opposite end of the head from the tumor or, even more tragic, had failed to identify the lesion because its consistency offered no clue to the exploring needle. Luckily, lung cancer was not common in those days, for it never occurred to us to get a film of the chest first in every case of suspected brain tumor. Prior to the advent of x-ray control, orthopedics consisted of bone setting — no more Unfortunately, there are no figures to tell us how many mothers have died because no one knew that some abnormality of the feto-pelvic size or position made delivery impossible, or how many unnecessary Caesarian sections have been done because someone could not resort to roentgen means to prove that such an impediment did not exist. Through history much genetic material must have been lost and much personal tragedy inflicted through lack of ability to gain information

There is no point in belaboring the issue further In the words of the Declaration of Independence, "We hold these truths to be self evident"

Equally self-evident is the fact that ionizing radiation is damaging. My first lesson in radiology as a student of the art and my first dictum to my own students was and is, "The only safe x-ray machine is one that is turned off, and the only safe radium is that which is inside an adequate lead block" The first skin damage was noted and reported within months after the discovery

of x rays and radium. Radiation induced carcinoma and anemia were recognized within a few years The leukemogenic effect and the genetic effects have been known for over a quarter of a century The so-called law of Bergonie and Tribondeau that sensitivity to radiation is inversely proportional to the degree of differentiation was formulated over 50 years ago, largely on the basis of observations of the effect of radiation on embryos. These truths we also hold to be self evident.

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pointed out, ". . . no agent that can modify the internal environment or organic integrity *of the body can be used without* hazard." We must admit that we know precious little about the genetic effect of many of these agents, especially as they may act in concert with ionizing radiation.

It is with regard to the genetic damage to the race that we come straight athwartships of the most serious moral and philosophical problems Is the well-being of the individual paramount or subordinate to that of the race or group? Granting that this is not an all-or-none proposition, then what degree of risk may I take with one for the benefit of the other? What profits it the unborn children if I destroy the parent? Or one may even argue thus. The individuals most likely to require extensive medical exposure are those who already possess weaknesses rendering them less fit to meet the exigencies of the present world. Reducing the viability or fertility of these individuals will tend to help the race while at the same time alleviating their personal suffering Accurate knowledge of the average number of ionizations in the gonads necessary to produce 1 or 2 or 10 mutations would help in assessment of the risk but would not resolve the moral issues at stake. And these issues we must continue to face as we have always faced them The problem is not new It is simply bigger.

Somatic damage to the individual poses slightly different problems The evidence for a no-threshold, strictly linear response relationship is less convincing than in the case of the genetic damage. It appears that there is great variation in age response or organ response as well as considerable *dependence upon the rate of administration* Here, definite data is of the utmost practical importance Unfortunately, all we have is suggestive data, and all we can say is that the available data seem to fit a pattern This pattern appears to have something like the following form

For genetic effects there is no threshold and no recovery The problem affects persons only from the time of their conception to the time when they have conceived their last child In the aggregate, this means potentially fertile men and women up

to the age of 35 or 40 years The magnitude of the risk is surmised only in terms of a doubling dose thought to be in the neighborhood of 50-80 roentgens

Carcinogenesis, including leukemogenesis, while having some sort of linear relation to dose, appears to be also influenced by age and rate of administration Alice Stewart's figures suggest that at some time during embryonal life a slight effect may be produced by as little as 2 to 4 r Simpson and Hempleman's studies of infants indicates a similar effect from doses of 50 to 200 r. Data given by Court Brown, Warren, Lewis and others suggests that to get the same incidence of neoplasia in adults, it may be necessary to give 200 to 500 r or more, depending upon the organ being studied, the dose rate, and other factors. In this regard, it should be pointed out that the relative volume dose has received comparatively little attention, and it is possible that the wide spread between Stewart's embryo figures and Court Brown's adult doses is wholly explainable on this basis In any event, it is evident that again, and regardless of exact quantitative dosimetry, the critical segment of the population is the young group They may be more sensitive and certainly have longer to accumulate a damaging dose and a longer time in which to suffer from the effects

Hence, we return once again to the moral and philosophical or ethical aspects of radiation exposure Ionizing radiation may be looked upon as just another dangerous weapon. Used wisely, it provides safety and wellbeing for the individual and the community Abused, it can destroy both. As *with* a gun, one must not hesitate to use it when the need arises, but one must always take precautions to make sure that one *is shooting* a burglar and not one of the children Fortunately, this is much easier to do today than 50 years ago The availability of good training, greater knowledge of dosimetry, the development of better recording media, and increased realization of the hazards of the weapon have greatly enhanced our ability to shoot, metaphorically speaking, faster, more accurately, and with greater economy of ammunition In many fields, the use of ionizing radiation was of necessity somewhat profligate during the developmental stages,

pointed out, ". . . no agent that can modify the internal environment or organic integrity of the body can be used without hazard." We must admit that we know precious little about the genetic effect of many of these agents, especially as they may act in concert with ionizing radiation.

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# APPLIED RESEARCH TO DIMINISH MEDICAL-DENTAL RADIATION HAZARD

By

DAVID GOULD, M.D.

*Professor and Head, Department of Radiology*
*University of Arkansas Medical Center*
*Little Rock, Arkansas*

Several months ago I wrote a paper on the hazards of radiation, and judging from the reaction many people read it. There is much talk about the hazards of radiation. I am tempted to write a paper on "the hazard of radiation hysteria." I think this is a very definite hazard. As an example of what is going on, I started a mass x-ray survey in the early 40's, and over a period of 12 or 13 years, there were only two cases that came to my attention of people who were terribly worried about radiation. One was a girl in the Veterans Administration and as she was standing in line for the photofluorographic examination, she said, "I *can't do it. I'm* not going to go ahead and get that chest film because I'm allergic to radiation." I tried to convince her and finally succeeded, that radiation does not cause any allergic reactions. She had her chest film and we did not find any tuberculosis in that particular girl. Nothing happened for a period of about ten years, and when I was working in Baltimore, a lady called me and said that she wanted to borrow a geiger counter because some people in a hospital which was five miles away from her home, pointed an x-ray machine at her and she was receiving "harmful effects from these rays." This unfortunate woman was obviously mentally ill.

Nothing really perturbed me very much until the last few years. I could mention a dozen examples of people who have gone a bit too far in the direction of what may be called "radiation hysteria." For instance, as soon as we opened our new

but as Sosman has said, ". . . the ultimate objective of all of these very complicated and sometimes dangerous procedures is to learn enough about these conditions so that we can go back and refer our knowledge to the original, simple, uncomplicated examination and know more about what we are seeing and finding."

It has been suggested that there should be legislation limiting the amount of ionizing radiation to which a physician may expose a patient. I can think of no more unwise legislation that could possible be conceived. Had such laws been in existence for the past 25 years, for example, some of the most valuable knowledge ever gained from the use of ionizing radiation would never have been obtained, and none of the real damage would have been prevented.

The real solution to our problem lies in continued research into the detailed nature and magnitude of these hazards, continued education of the medical profession, scientists, and the laity, and calm, dispassionate consideration of all of the scientific, moral and ethical factors involved

*Dr Scott.* Dr. Eberhard, you understand the art of medical practice Thank you for a splendid presentation Would anyone like to ask Dr. Eberhard a question? The general discussion will be deferred as was done this morning, but feel free to ask questions.

On the one hand, the radiologist says radiation is good and on the other hand, the geneticist says radiation is bad. They probably are both right. Radiation, in common with any other form of energy, is both good and bad. It depends upon how it is used. In my opinion, in the hands of a well-trained radiologist, radiation is at least 95% beneficial and less than 5% harmful. This figure is arbitrary. It may well be 99% on the plus side and only 1% on the minus side. The sum total of human comfort, happiness, longevity and benefit derived from radiologic diagnostic and therapeutic procedures can never be measured. If one compares the mortality statistics of 1900 with the mortality statistics now, you will find that at least 20 years have been added to the human span of life. Advances in modern medicine have been an important factor in this improvement. Many of us here are trying to quantitate the bad effects of radiation. Studies should certainly go forward to find out exactly how much harm is done. Since there is a hazard in the use of radiation, even though it has not been quantitated, it behooves the radiologist to do everything possible to minimize this hazard, both somatic and genetic. What can be done from a practical point of view to reduce this hazard to a minimum? Without an appreciable outlay of money a trained radiologist can reduce the hazard 50% by following these simple rules.

(1) Use the more efficient higher kilovoltage and lower milliampere techniques.
(2) Test equipment periodically for leakage and output.
(3) Use at least two millimeters of aluminum filtration.
(4) Use field limiting cones and diaphragms as much as possible.
(5) Choose the fastest, practicable screen, film and chemical combination.
(6) Process films full time using active chemicals and proper temperature.
(7) Protect the gonads in patients below the age of 40.
(8) Ask yourself, "Is this examination important to the health and well being of the patient and what is the most efficient way to carry it out?"

Medical Center in 1956, an engineer was one of the many visitors in the Radiology Department. He told me, "you should get rid of all this equipment. It is a big investment, I know, but you ought to get rid of it because you are doing so much damage to the future generations with radiation." I talked to him for about an hour and finally he was comforted

Yet, another instance: There was a technician in our department who wanted to take some films on a pregnant dog. The particular person who owned the dog said she would not allow these films to be taken because a friend told her that "pregnancy and radiation are a bad combination"

Just a week ago, a lady called me on Saturday night and said, "I would like to move to Arizona because I have hay fever and asthma. But, if I move to Arizona, it will be close to New Mexico and close to the atomic bomb tests Would it be harmful to my children?"

This kind of fear and confused thinking is frequent The questions from the lay public don't bother me quite as much as the "radiation hysteria" exhibited by medical people. An obstetrician told one of my secretaries who was pregnant that it was dangerous to work in a Department of Radiology because of possible injury to her unborn child I showed her the measurements that we made on our various radiologists and technicians Three-fourths of our staff have received only 1/20th of the maximum permissible dose, and that measurements on every one of our technical staff, with one possible exception, have been below the maximum permissible dose These are people who are working with the equipment and using radiation all the time The secretaries are so far removed from the diagnostic rooms that it wouldn't pay to try to measure the infinitesimal amount of radiation to which they are exposed

A pathologist once asked me if it would be safe to autopsy a patient who had received telecobalt treatments He thought that maybe this patient would, in some way, be radioactive and the autopsy might over-expose him There is considerable missionary work to be done to allay people's hysterical fear of radiation hazards

must be done on a voluntary basis. I do not believe it can be legislated

*Dr. Scott:* Thank you, Dr. Gould. Any questions anyone would like to ask Dr. Gould? If not, then we will proceed to our next subject, "Gonadal Radiation Resulting From Various Diagnostic Radiological Procedures," by Dr. Fred Hodges.

(9) Rules to follow during fluoroscopy:

a. Adapt your eyes for 20 minutes before fluor

b. Always wear protective gloves and apron.

c. The fluoroscopic tube — table distance shoul or greater.

d. Keep the shutters down to the smallest practi

e. Use the fluoroscope quickly and efficiently t motion and function and not as a screen p: Do not day-dream with foot on the switch.

In my own department I cannot do the best possib diminishing the radiation hazard because of the lack I am quite certain with unlimited funds the radiatio can be diminished to 25% of what it is today. For examp are rather sensitive and expensive film emulsions availal which allow the radiation exposure to be cut anywhere fr to 50%. There are available mirror optic photo-fluor equipment which exposes the chest with 60% less radiat conventional equipment Body section books which u ple layers of screens and film can reduce the exposure of what is used with conventional apparatus. With th the new 6 minute X-Omat developing apparatus, whi $32,750 at the present time, the service work and organi the department can be so arranged that the number of films can be cut to a minimum Technical quality ca proved so that repeat filming is a rarity

Now, how badly does society want to diminish the r hazard and how much are they willing to pay to obtain mate safety? Most hospital administrators working budgetary limitations cannot give us a free reign

I have talked to people in state and federal gov about this problem of radiation hazard Briefly, the a was put forth in this manner In order to reduce the r hazard to a minimum, let us develop as nearly a perfect ment of Radiology as possible. Let us train physicists, gists and technical people to check up on every radiation tor in the state. Let us advise doctors, dentists and ch ... the safest way to use their equipment Such a n

closely simulating the characteristics of human tissues, in which ionization chambers can be located in positions comparable to the ovaries and the testies, to the insertion of measuring devices into body cavities or into positions bearing standard relationships to ovaries and testes and held there during standard examination procedures, as well as the use of film badges worn by patients throughout the course of various types of examinations. Many of the recorded gonadal measurements have been standardized to single radiographic exposures. In some instances associated fluoroscopic procedures have been treated separately; in others bulked with radiographic dosage. It has been impossible, obviously, (in all instances) to reduce to a single common value factors of distance between the tube target and the gonad, the factors of tube current, kilovoltage, time, speed of film and screens employed, and the circumstances of film development All of these factors are enormously variable physically and when to this is added the habits of individual examiners, particularly in the matter of fluoroscopic procedure, the likelihood of achieving exactitude in the matter of establishing a firm value of gonadal absorption under all circumstances of diagnostic radiographic exposure seems remote indeed Some of the accumulated figures are further complicated by the use of specific gonadal shielding devices and it is obvious that if these devices are sufficiently massive, and extensive, gonadal absorption can be reduced to a very considerable extent

The variability of figures which are available in printed form is great indeed Even in the matter of radiation which reaches and is absorbed by reproductive cells in the *course of* chest examination, the values which have been reported vary widely. Some reporters indicate that gonadal absorption is greater under various conditions of chest examination for males than for females, although the reverse is ordinarily quoted Because so much has been written and said about genetic effects which may follow radiologic examination of the chest, it may be well to point out at this time that values in the neighborhood of one-tenth milliroentgen for males and approximately ten times that amount, or one milliroentgen for females comes close

# GONADAL RADIATION RESULTING FROM VARIOUS DIAGNOSTIC RADIOLOGICAL PROCEDURES

*By*

**DR. FRED JENNER HODGES**

*Professor and Chairman*
*Department of Radiology, University Hospital*
*University of Michigan*
*Ann Arbor, Michigan*

I had hoped to bring something in the way of exact figures that have been lacking up to date. I am sure now that that was wishful thinking of the worst sort. Our physicist and the younger men in the department who tried to help me in this matter have assured me that we simply are not able to present accurate figures for the actual dosage absorbed in regenerative cells.

The exact magnitude of the radiation absorbed by human gonads during various diagnostic procedures which employ the use of x-radiation would seem to be essential to a meaningful investigation of associated genetic effects. A great many attempts to provide factual data of this very sort have resulted in the accumulation of values which cover a wide range for supposedly comparable diagnostic procedures because of the very many variables related to the technical procedures themselves and to the methods of measuring absorbed radiation, which likewise are anything but uniform. Gratifying as it would be to have standardized gonadal absorption dose values for every conceivable type of examination, there is little likelihood that the degree of regimentation required to regulate such exposure with exactitude would be acceptable to practicing radiologists.

Attempts have been made to measure gonadal radiation under experimental and standard clinical conditions in a variety of ways. These range from the careful construction of phantoms

commonly employed, in which largely inescapable gonadal radiation is delivered in sizable amounts, involves patients who fall within the 0 to 30 year age group. By actual count 7 standard procedures which as done at our institution expose gonadal tissue to radiation in excess of 1 roentgen per examination constitute only 20% of the annual total number of examinations conducted, 12,908 in a total of 61,076. In the order of magnitude of

TABLE 1

SEVEN TYPES OF EXAMINATIONS YIELDING SURFACE DOSAGE IN EXCESS OF 1 R OVER THE GONADS

| | |
|---|---|
| Angiocardiogram | 1.5 r |
| Excretory Pyelogram | 2.25 r |
| Pelvimetry | 4.9 r |
| Lumbosacral Spine | 5.4 r |
| Upper Gastro Intestinal Examination (fluoroscopy plus films) | 5.7 r |
| Routine Spine | 5.8 r |
| Hips Pelvis | 8.8 r |

(Doses are given as surface values and obviously gonadal doses are measurably less especially in the female.)

skin dose over the gonads these 7 procedures are (Table 1) angiocardiogram (1.5), excretory pyelogram (2.25 r), pelvimetry (4.9 r), *lumbar* spine (5.4 r), upper gastro-intestinal examination (5.7 r), routine spine (5.8 r), hip and pelvis (8.8 r), it is obvious that the actual value of radiation absorbed by the gonads will be measurably less than the surface values listed. Taken as a group those patients subjected to these types of examinations, who at the time were 30 years of age or younger, numbered 3215, or 25% of the people so examined. Arranged in the order of increasing numbers of those who fall below the *age of 30, Table II*, the 7 examinations are listed as upper gastro-intestinal tract (12.5% age 30 and below), routine spine (23%), lumbar spine (25.5%), excretory pyelogram (29%), hip, pelvis (35.5%), pelvimetry (70%), and angiocardiogram (78%). Fortunately for all concerned the focusing of attention on methods and the use of devices to shield gonadal tissues during those examination *procedures* most likely to result in heavy gonadal absorption involves a relatively small number of patients

to representing an average figure from a large number of sources for the expected gonadal radiation absorbed during the roentgen examination of the chest using standard direct filming technic. These values will be increased by a factor of 5 or thereabout when the photofluorographic method employing refractor optics is used. It is convenient to use the rounded figure of 5 milliroentgens of radiation absorbed by the ovary in the course of a single photofluorographic exposure of the chest as the high value for gonadal radiation from chest examinations of all sorts. Using this convenient figure as the divisor, and 10,000 milliroentgens or the 10 roentgens of life-time radiation absorbed by gonads considered currently to be a tolerable burden from the genetic viewpoint, it will be seen that in the course of 30 years this type of chest examination could be repeated 2000 times before the agreed upon maximum allowable dose would be reached.

When types of examination involve bodily parts which are in close relationship to the gonads the magnitude of gonadal absorption is very much greater. Unfortunately, the clinical and experimental computations of gonadal absorption are even less uniform under these circumstances than are those for procedures which are directed toward the chest, but one can say in complete fairness that whenever the primary x-ray beam used for diagnostic purposes of necessity finds gonadal tissue in its direct path the values for gonadal absorption will be measurable in hundreds rather than in single milliroentgens. For example, pelvimetric examinations utilizing two exposures, one in anteroposterior, one in direct lateral projection, may be expected to result in the absorption of something in the neighborhood of 24 to 36 hundred milliroentgens, depending of course upon a variety of variables including prominently the bodily dimensions of the patient as well as the efficiency of photographic materials and screens.

One should not lose sight of the fact that the absorption of radiation by gonadal tissue is of importance only when it occurs in individuals who are still within the age group where reproduction is to be expected. Before one embarks upon any computation of the future genetic effects of gonadal radiation, it is important to take notice of the fact that only a fraction of the procedures

commonly employed, in which largely inescapable gonadal radiation is delivered in sizable amounts, involves patients who fall within the 0 to 30 year age group. By actual count 7 standard procedures which as done at our institution expose gonadal tissue to radiation in excess of 1 roentgen per examination constitute only 20% of the annual total number of examinations conducted, 12,908 in a total of 61,076 In the order of magnitude of

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(Doses are given as surface values and obviously, gonadal doses are measurably less especially in the female)

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TABLE II

FREQUENCY OF UTILIZATION OF EXAMINATIONS CARRYING HIGH GONADAL DOSAGE—1956-57

| *Examination Type* | *Times Used* | *Pts. Under 30 Years* | *% Under 30 Years* |
|---|---|---|---|
| Upper Gastro-Intestinal Examinations | 4801 | 602 | 12.5% |
| Routine Spine | 1132 | 260 | 23.0% |
| Lumbosacral Spine | 2122 | 541 | 25.5% |
| Excretory Pyelogram | 1795 | 525 | 29.0% |
| Hips, Pelvis | 2538 | 900 | 35.5% |
| Pelvimetry | 370 | 260 | 70.0% |
| Angiocardiogram | 147 | 115 | 78.0% |

in any one working day, enhancing the likelihood of achieving the increased degree of gonadal protection which is so highly desirable.

In the interests of long range genetic experiments and observations by which man may hope to determine with reasonable accuracy the magnitude of the hazard presented by various diagnostic procedures employing the use of radiation it is desirable that efforts shall continue to obtain values for gonadal radiation currently being absorbed by reproductive cells from large patient populations in the course of clinical radiologic practice. As matters stand presently it is unlikely that anything more than the extremes of gonadal radiation expressed in the broadest of terms can be derived from accumulated and accumulating clinical experience.

*Dr Scott:* Thank you, Dr Hodges. That was a very helpful presentation. Any specific question for Dr Hodges?

# RADIATION REDUCTION IN OBSTETRICAL RADIOGRAPHY

By

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*Indiana University Medical Center*
*Indianapolis, Indiana*

There is no medical field in which the reduction or limitation of diagnostic x-ray exposure is better justified than in obstetrics Regardless of which side of the fence you want to take on this point, I think you'll admit that when you are doing diagnostic work today on an obstetrical patient, it at least makes you nervous. The potential hazard of excessive radiation dosage is both genetic and somatic because prenatal radiography involves simultaneous gonadal exposure of both mother and fetus, as well as total body irradiation to the embryo at a time of major organogenesis

The radiographic procedure itself imposes a maximum of undesirable factors on the radiologist The large physical dimensions of the patient necessitates a greater dose of irradiation while the use of slow screens for fetal bone detail, high density grids to absorb scattered radiation and multiple views significantly increase the exposure required Of the genetically significant radiation received by humans from medical uses, approximately 20 to 30% is said to be contributed by obstetrical radiography and I am quoting figures that Dr. Fred Hodges showed today from Laughlin and Pullman

Radiography of the pelvis in women who are not aware of an existing pregnancy is fraught with possible hazard to the embryo Dr Russell has demonstrated in mice that there are critical periods of embryogenesis, particularly between the second and sixth week of gestation when doses as low as 25 r can produce abnormal developments in the first offspring More alarming is

the report of Stewart, indicating that children born of women subjected to x-ray pelvimetry during pregnancy develop leukemia in the first ten years of life twice as frequently as non-irradiated offspring. It is estimated that these fetuses received about 2500 mr. of total body irradiation. Recently a similar report has been published at Tulane University (I don't know the author nor have I seen that report) On the other hand, no leukemia has been reported during the first decade in Japanese children who were irradiated *in utero* by the Hiroshima atomic bomb.

From the geneticist's standpoint, who is concerned with the production of gene mutations, any amount in excess of natural background radiation is capable of genetic injury. The geneticist is, therefore, entirely consistent in recommending that the fetus be protected from all radiation.

It is obvious that medical urgency frequently makes such a complete interdiction impractical. Nevertheless, radiography of the pregnant abdomen should be done only for compelling reasons. *In such an instance, the radiation exposure must be minimized* by every means at our disposal. There are several ways of achieving this. These may be grouped as general, technical and procedural considerations

We were interested in finding out where we stood on this matter for two purposes, one to study what the methods were effective in reducing the dosage that we were using and secondly in seeing how far it could be reduced and still get something that looked like a satisfactory diagnostic result

## GENERAL CONSIDERATIONS

1 *Avoid routine roentgenologic procedures*.—This consists of talking yourself out of unnecessary examinations as routine procedures as opposed to the idea of just doing these as part of the general workup of an obstetrical patient The routine use of chest surveys, pelvimetry, pyelograms, dental films, skeletal surveys, and fluoroscopy should be postponed during pregnancy. The yield of these procedures does not warrant such use.

2. *Avoid roentgen examination of the pelvic area during*

*early pregnancy*.—Whenever possible, roentgen exposures of the pelvic area in women of the childbearing age should be restricted to the two weeks following the last menstrual period to preclude the possibility of fertilization having occurred.

3. *Proper equipment and personnel.* A high capacity (300 MA-120 K.V.) generator and tube will permit short exposures, longer tube film distance, efficient collimation and heavy filtration. Technicians must understand the advantage of every desirable factor employed, because the greatest exposure reduction results from accomplishing the correct technique on the first attempt without repetition. Immobilization devices and phototiming prevent motion and overexposure.

4. *Protective shielding*.—A lead screen of 2.0 mm. lead thickness may be used to cover the fetus and the maternal gonads whenever their exclusion does not decrease the usefulness of the examination, i.e., pelvimetry.

5. *Consultation*.—Consultation between obstetrician and radiologist before roentgen examination of the pregnant abdomen will result in a higher yield from fewer exposures. Radiologic examination should be a confirmatory maneuver, not a means of arriving at a diagnosis by exclusion.

## TECHNICAL CONSIDERATIONS

I have listed the technical factors which may be utilized to reduce the amount of radiation *necessary* for a satisfactory diagnostic radiograph.

1. *Collimation of the primary beam*.—The use of double diaphragm rectangular aperatures will reduce scattered radiation as much as 30% over circular fields.

2. *Use of longer target film distance*.—Due to the improvement in percentage depth dose, the *same amount* of radiation can be delivered to the film with as little as two-thirds of the skin dose when longer distance is used.

3. *High kilovoltage technique*.—The use of 100-120 kilo-

voltage techniques will reduce the entrance dose up to 50% without loss of film density.

4. *Added filtration of primary beam.*—The addition of 2 to 6 mm. of aluminum (depending on kilovoltage level) to the primary beam will reduce the entrance dose as much as 75% over the unfiltered beam. Gianturco et al point out that filters are needed because of the shape of the current furnished by present day valve-rectified generators They could be completely eliminated by the use of a square wave such as given by a dynapulse unit.

5. *Use of high speed intensifying screens.*—Fast screens will reduce the necessary radiation dose at the film two to four times with negligible loss of detail.

6. *Use of extra-fast film.*—A reduction of 20-50% in film dose, depending on screen type and kilovoltage range, can be obtained by the new faster film emulsions. The resultant roentgenograms show less latitude and a shorter scale of contrast. We used Eastman Royal Blue and Ilford Red Seal film.

7. *Improved film development.*—A reduction of exposure in the range of 20% can be accomplished by processing films in phenidone hydroquinone developer (Picker or Ilford) for 5 minutes at 68 degrees Fahrenheit instead of conventional metol hydroquinone developer.

8. *Low absorption cassettes.*—By decreasing the thickness and absorption of the cassette used in obstetrical work, the dose may be lowered as much as 10% to 20%.

9. *Lower Grid opacity.*—Grids of higher ratio and density, necessary to maintain contrast in high K.V. techniques offset to certain extent the reduction in patient dosage. The use of 6:1 to 12:1 range of grid ratios is a desirable compromise according to the technique employed Nevertheless, if grid opacity is not balanced against the K.V. employed, unreasonable high patient dosage or technically unsatisfactory roentgenograms will result

10. *Differential filters, frames and centering devices.*—Wedge filters will reduce regional exposures to parts of uneven thickness. Opaque frames with various-shaped apertures will restrict the radiation to areas of interest A reliable illuminated

beam director will aid in precise centering of the coned beam on the patient and film.

It should be noted that the factors of collimation, target distance, high K.V., and added filtration chiefly reduce the entrance skin dose while maintaining relatively the same exit or film dose. While these factors cause a great reduction in skin dose, this improvement in dose is steadily reduced through the depth of the patient, becoming of little value at and beyond depths of 20 cm There is, however, a definite reduction in dosage to the fetal and maternal gonads which lie slightly anterior to the midsagittal plane.

One reaches an irreducible end point, however, where only a reduction in film-dose requirement will allow further reduction of the dose to the gonads Such effect is accomplished by the factors relating to increased screen response, film speed, more radiable cassettes, and low-density grids Each of these provides a decrease in the amount of radiation required at the film which, in turn, means a reduction in skin, integral, and gonadal dosage. It is wise to investigate and adopt all possible measures which permit recording a film image of desirable quality with the least exit dose

If an additional grid could be interposed above the patient and perfectly aligned with the conventional grid, (the so-called sandwich grids), it would prevent the passage through the patient of primary radiation destined to be absorbed by the second grid. In the same way, a wedge filter over the thinner anterior portion of the lateral pregnant abdomen is a better choice than a slow screen in the cassette for equalizing the density of the image, because it prevents delivery of unneeded radiation to the patient.

## PROCEDURAL CONSIDERATIONS

The majority of obstetrical radiographic procedures utilize from 2 to 4 projections Of these, certain views contribute more gonadal radiation than others The lateral view may give up to 5 times as much as the AP, the AP twice the PA and the pelvic

inlet view as much as two-thirds of the conventional three-film pelvimetry technique. There is practically no difference in the gonadal dose of AP or lateral exposures if taken only for soft tissue visualization because no attempt is made to penetrate the increased density of the pelvic bones. Elimination of non-essential views reduces radiation immediately by a greater amount *than would result from improvement in technical factors.*

Selection of a single projection which provides a broad spectrum of diagnostic obstetrical information is very desirable as a pilot study I have always entertained the idea that if one could boil the procedure down to one view that would do everything—sort of an all purpose technique, that perhaps this had some merit A single erect lateral view of the abdomen and pelvis provides the most useful information in this regard for the following reasons:

1. Visualizes entire fetus and uterus
2. Demonstrates placental location
3. Permits recognition of fetal malposition or abnormality.
4. Allows the diagnosis of fetal death.
5. Permits an estimate of fetal maturity.
6. Furnishes pelvimetry diameters of anteroposterior bore birth canal.
7. Provides detection of extrauterine gestation and multiple pregnancy.
8. Demonstrates degree of centering, descent, and presentation of fetal head in pelvic inlet
9. Supplies definite indications for additional radiography

Figure 1 shows a diagram of the positioning technique for the lateral erect view, as well as for the AP erect view and the PA prone view The isometric ruler is superimposed in the midline plane of these projections.

*In order to* include the entire area of diagnostic interest in larger patients, a special 17" x 17" cassette may be employed with a standard grid tray. Figure 2 demonstrates this home made cassette.

When it is determined that a frontal projection is necessary there are certain advantages in utilizing a PA view with a com-

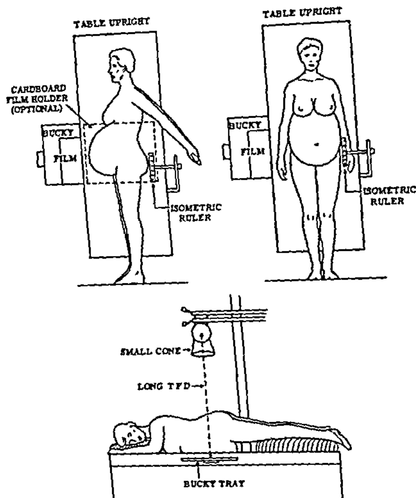



Figure 1

pression band as advocated by Bewley. This reduces the thickness of the patient up to 10 cm. over the AP supine view with a correspondingly smaller exposure requirement. The maternal gonadal dose is reduced about one-third due to shielding by the pelvic bone, and the fetal gonad dose is up to 10 times smaller. The latter reduction is more because the fetal gonads lie on the side opposite the entrance of the primary beam when the PA projection is used The PA view also provides an improvement

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Figure 3

Figure 4

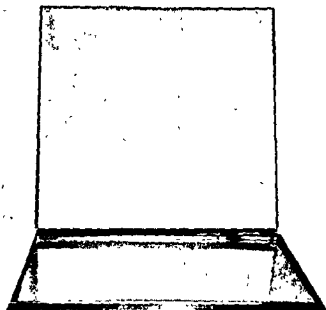


Figure 2

in the detail of the fetal parts due to the shorter object film distance. Obviously, the PA view also may be used as a pilot study and pelvimetry of the transverse diameters obtained from it The integral radiation dose delivered is only 25% of the lateral view.

Clayton et al have pointed out that in cephalic presentations the fetal gonad lies high in the fundus anteriorly. In addition, the maternal ovaries are carried to a point about 7.0-8.0 cm. above the iliac crests in the midcoronal plane by the expanding uterus. One may take advantage of these facts to exclude the fetal and maternal gonads from the primary beam when pelvimetry alone is desired by restricting the exposure closely to the pelvic area (Figure 3). This may be nicely accomplished by placing a lead shield with a 5″ x 5″ aperature and a 2″ center strip over the patient in the frontal and lateral projections to assure that only the bony structures of the pelvis are exposed to the primary radiation (Figure 4). Furthermore, since the semi erect view of the pelvic inlet (Thom's projection) delivers twice as much radiation to the fetal and maternal gonads as the frontal or lateral

pelvis, lumbar spine and a leather fetus and placenta were placed within the phantom. The intervening space was filled with rice (Figure 5). Holes were made in the anterior and lateral surfaces of the phantom to permit the introduction of a 25 r Victoreen ionization chamber for obtaining radiation doses in the midsaggital and midcoronal planes at the level of the pelvic

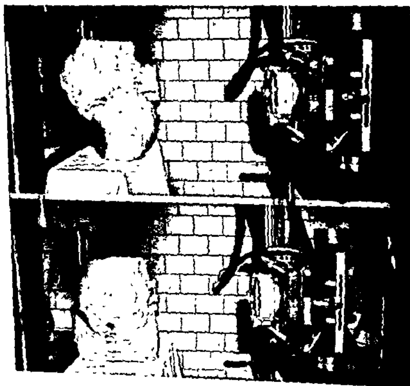


Figure 6

inlet. Entrance and exit doses were also measured (Figure 6). Because the standard ionization chambers do not accurately record the high intensity short exposures used in diagnostic procedures, radiation of the same quality was given with a water cooled tube using lower milliamperage and larger exposures. The actual exposure doses were then calculated from these determinations. Any inherent error in these dose measurements is likely to be the same for all readings.

views, this technique should be avoided. As a corollary to this, when the diagnostic information desired pertains only to the contents of the pregnant abdomen, no attempt should be made to penetrate the density of the pelvic bones, and the exposure decreased to that amount necessary to illuminate the soft tissues.

## EVALUATION OF LOW DOSAGE TECHNIQUE

Comparative radiographs were obtained on full-term pregnancies utilizing two techniques. Technique 1 consisted of the following factors: 70-90 K.V., 1 mm. Al. filter, 40" TFD, 6:1 grid ratio, par speed screens, average speed film (Eastman Blue Brand, DuPont 508) and a circular cone Technique #2 consisted of 120 K.V., 3 mm. Al. filter, 40" TFD, 16:1 grid ratio, high speed screens, high speed films (Eastman Royal Blue or Ilford Red Seal) and a double-diaphragm rectangular cone Standing lateral and prone PA views were obtained in different patients with both techniques

In addition, a phantom in the shape of a maternal abdomen was cast from a patient. This was made of dressmaker's paper, which showed no significant absorption of radiation A bony



Figure 5

It will be noted that the skin dose of the PA view using the low dosage technique (II) is 300-400 mr as compared to 2400-3250 mr for the conventional AP views (I) while the midpelvic doses are 51-73 mr as compared to 190-253 mr. The lateral view with the new technique required a skin dose ranging from 1170-1730 mr and a midpelvic dose of 165-250 mr, while the standard technique required skin doses of 7750-8720 mr and midpelvic doses of 460-524 mr.

Actually we were able to obtain many PA views with the low dosage technique with as little as 10 MAS. For the average sized lateral, the exposure was reduced to as little as 50 MAS and for the large patient about 75 MAS.

We also noticed that when we switched to the low dosage technique, the exit doses were just half of the values obtained on the standard techniques indicating that the recording media was twice as sensitive to radiation The resulting roentgen image was of comparable density, but somewhat grainy and showed a shorter scale of contrast.

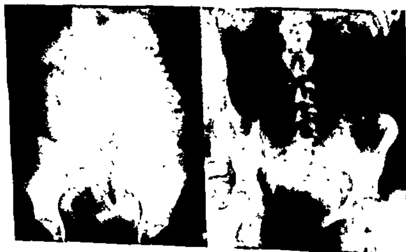


Figure 9

(Figure 9). This is a comparison of the AP with the old technique on the left and a PA with the new technique on the

The roentgenographic techniques used for comparable film

TABLE I

COMPARISON OF TECHNICAL FACTORS

| *Technique* | *KV* | *Filter* | *FFD* | *Grid Ratio* | *Screen Speed* | *Film Speed* | *Type Developer* |
|---|---|---|---|---|---|---|---|
| I AP | 80 | 1 Al | 40" | 6:1 | Med | Reg | Metol* |
| I Lat. | 90 | 1 Al | 40" | 6:1 | Med | Reg | Metol* |
| II PA | 120 | 3 Al. | 40" | 16:1 | High | Fast | Phenidone** |
| II Lat | 120 | 3 Al. | 40" | 16:1 | High | Fast | Phenidone |

*Kodak Regular
**Picker Pix, Ilford PQX 1:2

Figure 7

densities are given on Figure 7. Comparison of the entrance, mid-pelvic, and exit doses measured with each technique are given on Figure 8.

TABLE II

COMPARISONS OF RADIATION DOSAGE

| *Technique Exp* | *Exposure in MAS* | *Skin Mr/Exp* | *Midpelvis Mr/Exp* | *Exit Mr/Exp* |
|---|---|---|---|---|
| I AP | 150 | 2100 | 190 | 28 |
| I AP | 200 | 3250 | 253 | 25 |
| I Lat | 100 | 7750 | 160 | 29 |
| I Lat | 150 | 8720 | 321 | 32 |
| II PA | 15 | 300 | 51 | 8 |
| II PA | 20 | 400 | 73 | 10 |
| II Lat | 50 | 1170 | 165 | 11 |
| II Lat | 75 | 1730 | 250 | 12 |

Figure 8

may be utilized collectively or singly. Not all of them are useful all the time

1. The potential genetic and somatic radiation hazard in obstetrical patients stems from the simultaneous gonadal exposure of mother and fetus and the total body irradiation of the fetus

2. Obstetricians and radiologists should discipline themselves to avoid any routine or unneccessary roentgen procedures of the abdomen and pelvis in women of childbearing age, to avoid radiography during early pregnancy, to use well informed technicians, and to select, through consultation, the safest procedure with the highest diagnostic yield

3. Clinical experience has shown that roentgen pelvimetry is infrequently necessary for obstetrical prognosis. Its use should be limited to those cases in which the exclusion of dystocia is indeterminate by other clinical means

4. The use of high kilovoltage, heavy filtration, efficiently collimated beam, fast screens and films, full phenidone film development, and proper grid ratios will achieve the lowest radiation doses to the skin, gonads, and fetus.

5 The use of a single upright lateral view on a large 17" x 17" cassette covering the pelvis and abdomen will suffice as a single pilot exposure yielding a broad diagnostic return This can be supplemented with a compressed prone PA abdominopelvic view when indicated These two views, providing a complete range of obstetrical roentgenologic diagnosis, may be obtained with as little as 250 mr. delivered to the midpelvis of an average sized patient at term This represents over 75% reduction of the radiation dosage required with standard two film techniques and even more so over techniques which require additional films

6 For fetal survey only, a lightly exposed PA or lateral abdominal radiograph can be made with a total exposure of only 15-25 mr to the midline.

7 In late pregnancy, the maternal and fetal gonads are located well above the crests of the ilia in cephalic presentations. When the examination involves pelvimetry only, restricting the

right on the same patient. The right film was made with 15 MAS, the one on the left with 200. That is on Royal Blue film or on Ilford. I am not sure which that is. We found them not too far apart.



Figure 10

Figure 10 is the comparison of two lateral views on the same patient. We were trying a wedge filter over the front of the abdomen. This is the old technique on the left, the new technique on the right and reproduction of this is perfect, although as you notice, the pelvic area is not heavily penetrated. However, we felt we could make pelvic measurements from this if necessary. We could see the head. We could see placental position on the posterior wall of the fundus and we would have been able to diagnose fetal maturity pretty well. Admittedly, we have perhaps given up something here in the long run, but if you are not a perfectionist, I think you can still get a satisfactory diagnostic yield and a handsome reduction in radiation exposure with this low dosage technique.

## SUMMARY AND CONCLUSIONS

Low exposure obstetrical radiography involves the application of certain general, technical and procedural factors. These

# SUMMARY OF CONFERENCE WITH REMARKS ON THE GENETIC HAZARD OF DIAGNOSTIC RADIOLOGY AND MEANS FOR REDUCING IT

By

DR. PAUL C. HODGES
*Professor and Chairman Department of Radiology*
*University of Chicago*
*Chicago, Illinois*

I brought a seven page manuscript and six lantern slides, but I have decided to abandon them because most of the things I was going to say have been said four or five times today. I jotted down notes as you gentlemen talked and it seems to me that certain points have come out that everybody here admits. First, radiation can cause genetic damage None of us learned that for the first time today but we learned a lot more about it. Second, man is subjected to much unavoidable background radiation but the mere existence of unavoidable background does not excuse the addition of avoidable radiation. These are things we all know but it is well to have quantitative information about them

The surveys that have been made on estimated gonadal doses for the entire population exaggerate the situation in diagnostic radiology They are full of errors which the people who made them must recognize Anyone who has had anything to do with radiation therapy knows that for several decades after it began to be important, we had only rubber yardsticks with which to measure the dose The earliest measuring devices were not ionization chambers and the first chambers that became available were not independent of wave length Anyone who attempts today to compare doses recorded thirty years ago at another institution with those recorded today in his own institution knows that this is a waste of time Even after thimble chambers were improved

beam to the pelvic area and avoiding the use of the inlet view (Thom's) prevents direct irradiation of both gonads.

*Dr. Scott:* Dr. Campbell, that was a fine study and clearly presented. Examinations and reports of this type are most helpful in minimizing radiation effects and we need more like it. Would anyone like to ask Dr Campbell any questions about his technics?

I have asked Dr. Hodges to give as much of his paper as he wishes, and in addition to summarize the major points brought out during this Conference. At the conclusion of his talk, the meeting will be open for general discussion.

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it was some time before familiarity with them reached the point where recorded dosage was dependable.

We are in almost that same situation today in diagnostic radiology. Almost everybody has attempted to measure the doses in diagnostic radiology with chambers that have been developed for therapeutic radiology and these therapy chambers are almost as inaccurate in diagnosis as the earlier measuring devices were in therapy. I was relieved when I learned that the pressure for bigger and better surveys had eased so that public and private money probably now can be used to find means for making diagnostic radiology as safe as possible rather than for additional surveys to find out how bad it can be

The existence of unavoidable background radiation is no justification for permitting unavoidable radiation but there is considerable variation in background, about which we could do something if we wished to. For example, we do not and should not make it illegal to move from a frame house in San Francisco to a brick house in Denver nor do we make it illegal to go up to Pike's Peak and sit on a rock It follows, therefore, that we should not worry about the gonadal dose delivered in making a chest microfilm of an adult male since that dose is identical with the additional background he would acquire if he had come from a frame house in San Francisco to spend 3.6 days in a brick house in Denver, to say nothing of the dose that would be incurred if he went on up to Pike's Peak and sat on a rock

Above everything else, I was impressed with the slight divergence of opinion between the geneticists and the radiologists. It is the same old story — people misunderstand when they are quoted second or third-hand in the press and understand one another more easily when they sit down together I detected little difference between the extreme genetic view and the extreme radiologic view

Dr Gould and I were discussing at lunch a question that is frequently asked: "If the human race came out of the trees and learned to use its hands instead of its toes all because of mutations, then why don't we use x-rays deliberately to expedite mutations." Of course, the answer is that whether they be natural or

induced most mutations are deleterious and only a few advantageous. With irradiated seed corn, one may kill off the myriads of misfits and save only the desirable mutations, but no one seriously believes that these tactics should be applied to man.

Now as to precautionary measures that may be taken to reduce the tissue dose in diagnostic radiology. Above everything else, there is the avoidance of unnecessary examinations. Many x-ray examinations being done today in my opinion are not necessary. At our institution, we are called on constantly to repeat examinations of the stomach, colon, gall bladder, etc., not because the doctor believes they are necessary but that the patient wants them and is furious if they are not provided. Within recent weeks one of our young men diagnosed a peptic ulcer on a patient who was sent back on the next day for repetition of the examination. When I inquired as to the cause, my colleague who had referred him said, "Before I sent the patient to you I told his relatives that I didn't think he had a peptic ulcer and so when I got your report I had to call his wife and son by long distance. They reminded me that I had said that no ulcer would be found and I said the radiologists thought they had found one but, of course, would check their findings." Because of this commitment there seemed to be no way out and we had to go on with an unnecessary repeat examination.

We should do everything possible to avoid unnecessary examinations but the radiologist himself can do little — it is the referring physician who must take the *responsibility* of denying to his patients examinations which, in his opinion, are unnecessary.

I was interested in what Dr. Campbell *had* to say about pelvimetry. It was splendid to see what can be done to reduce the dose when pelvimetry has to be done but the important thing is to recognize that *not* often does it have to be done.

Medical students have been taught *manual* pelvimetry for a hundred years. If it were an accurate means of determining the size of the pelvis, of course one should *never* do x-ray pelvimetry. As a matter of fact, however, manual pelvimetry is a feeble tool and *if* it is necessary to measure the pelvis accurately x-ray pelvimetry is the method to be employed. Fortunately, it is seldom

necessary to have this information and the trial of labor usually is a dependable guide. In our hands, pelvimetry has been used less and less in the past decade, not because we fear to use it but because we consider it necessary only in exceptional cases

Dr. Campbell and others have told you the advantages of high voltage, heavy filtration, fast screens and fast films. Dr. Friedell and I were discussing this matter of fast screens and films and we wonder whether the geneticists know what has happened in this field.

Radiologists have long known that the tissue dose could be reduced by using faster films and screens but the price we paid was deterioration in detail and most of us were not brave enough to apologize for what we considered relatively poor-quality films in order to reduce tissue dose. Today we are re-educating ourselves and our aim is clinically satisfactory films with minimal tissue dose rather than films of maximum technical quality regardless of dose

It is strange that no one has talked of image amplification Ten years ago we would have bubbled over with enthusiasm as to what image amplifiers were going to do toward reducing the tissue dose I wish that the predictions (and some of them were mine) had come true, but they have not. Almost all of us are working with image amplifiers of one sort or another They have a limited usefulness but in their present stage of development have not accomplished the thing that we thought they would We would have hard work getting along without them but they have not cleaned up the problem on a large scale

What are other steps we can take to further reduce radiation dose? Probably the most important thing is the restriction of the size of the incident beam For many years we have done all of our fluoroscopy and spot filming with a screen that measures 4-1/4 by 7 inches Every visiting radiologist who looks at it shakes his head and says, "You can't do an adequate examination with such a small screen " Of course you can't until you have tried it. When we built the instrument, we provided it with a large screen and were going to use the little screen only for spot

films, but after a year or so we discovered that the big screen was gathering dust and so we never use it any more.

Shielding of the gonads is extremely important. I thought you might be interested in seeing one of the devices we have developed (for description and illustrations, see *J.A.M.A.*, July 5, 1958, pp. 1239-1240). The shield is placed between the patient's legs, the technician locates the pubic symphysis, places the tip of the lucite at that level, and then lowers the shield until it is in contact with the sheet covering the patient. The distance between the tip of the lucite and the lead is such that in the completed pelvic film the lead, though covering the testicles, does not obscure any of the pelvic bones.

Phantom measurements indicate that in pelvic filming done at 80 KV, 100 MA with 2 MM al filter, a target-film distance of 40 inches and a 16 to 1 grid the dose to the testes protected by the shield is approximately 5% of what it would be without it.

*Dr Scott*: Thank you, Dr Hodges. I am sure you will all agree that Dr Hodges is a master at summarizing. Furthermore, your testicular shield is a practical and ingenious device. You always manage to produce something constructive.

I want to emphasize the point brought out by Dr Eberhard that the decision as to what is best for the patient must remain the responsibility of the attending physician. It is he who must make the decision as to what is best for the patient and what he must have in the way of examinations. Any other basis destroys the proper relationship between the patient and the attending physician. This means all physicians must be more intelligently informed about genetics, radiobiology and the proper indications and use of diagnostic radiology and the possible hazards. Furthermore, the information the geneticists and radiobiologists have presented here is not the voice of gloom and doom for diagnostic radiology. It is helpful knowledge that will enable us to do a better and more careful job. It is a challenge and a stimulus for us to improve our techniques, to develop new protective devices, and to assist our referring physicians to make a better selection of the patients for radiographic examinations.

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port is decreased When they are interested and crowd around, we hold the screen over their gonadal region. When the foot switch is actuated and the screen glows, they are astounded and move back quickly. Also, in Louisville, so far as I know, there is not a pediatrician who owns an x-ray machine or a fluoroscope.

*Dr. Mickey*: In respect to reaching the students early in the stage of their training, I should like to propose that we geneticists get a shot at them in pre-medical school with courses in genetics I think that it ought to be a required subject. All pre-medical students should have an elementary course in genetics and all medical schools ought to have a required course in advanced genetics.

*Dr Brues*: I would just like to pronounce a plague on both houses I don't think that medical students get enough genetics on the whole, but a few get it very well in some places. I also think Ph D.'s in biology don't know enough about pathology and cancer because cancer is too often not considered as a broad biological problem I think we have to correct both of these deficiencies

*Dr. Tice*. Dr Scott, I want to thank you and your Committee for your excellent program I think it has been a wonderful thing for us to get together and discuss these problems I have been thinking about the book laminagraph Dr Gould mentioned We have had ours for about eight months We take a lot of laminagraphs, whereas previously we were taking about seven exposures, now we make only one I would like to ask two or three questions of Dr. Paul Hodges (1) Do you think an apron type of girdle that goes around the patient's waist is effective in protecting the patient's gonads? (2) Do you think that it is practical? (3) The premature aging process from radiation as discussed by the geneticists and the report of Dr Shields Warren on the shortened life span of radiologists, can we overlook these hazards? Is that nothing to worry about as far as we radiologists are concerned? And last, I have heard nothing mentioned about Dr Ira Kaplan's work with which you are all familiar. Dr Kaplan, for over a period of over twenty-nine years irradiated 660

about this problem?" For over fifty years, they have been and still are very seriously concerned about it. The American College of Radiology, through their Commission on Units, Standards and Protection, of which Dr. Richard H. Chamberlain is Chairman, just produced a booklet, "A Practical Manual on the Medical and Dental Use of X-rays With the Control of Radiation Hazards." Miss Sampley will give a copy to each of you. This manual is being distributed to all practicing dentists, physicians, internes and residents in the United States as an act of public service. The American Roentgen Ray Society, the Radiological Society of North America and the Section on Radiology of the American Medical Association all have symposia and Instructional Courses on this subject at their annual meetings Special bulletins and reprints of various articles are circulated to their members. My Commission on Public Relations of the American College of Radiology is now preparing an educational motion picture on radiation hazards and their control for the medical profession These are some of the active programs that are now underway

Dr. Paul Hodges' discussion and summary is now open for general discussion

*Dr. Pirkey:* There is one point that hasn't been brought out today and that has to do with the teaching of medical students They are the group we as radiologists have a chance to inoculate with the newer ideas and knowledge about genetics and the proper use of diagnostic radiology In our teaching program, I often state that any time a physician fluoroscopes a patient with out having his eyes adequately dark adapted, it is malpractice It is just like starting to operate on a patient without boiling your instruments for twenty minutes if you don't prepare your eyes for the twenty minutes. Another effective means for impressing the importance of using limited fluoroscopic fields on medical students is to use a small fluorescent screen. Bring the students in groups of eight to ten into the fluoroscopic room and talk to them in the dark until their eyes are dark adapted It is amazing how one can demonstrate scatter radiation around the side of the fluorescent screen with a piece of fluorescopic screen With the port opened, the screen is brighter and dims as the size of the

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other group of specialists by something in the order of a year, probably not statistically significant, but the radiologists had a longer life expectancy than the non-medical specialist. So I take it if you lose anything by being a radiologist, it is compensated by being a specialist

To go back to the question of direct radiation of the ovaries to induce ovulation. A rough computation, using mouse data and making several assumptions, would give about half a percent as the number of gross abnormalities in the first generation children from a dose of 100 r.

*Dr Paul Hodges:* Would this be added to the natural 1%?

*Dr. Crow:* Yes.

*Dr. Scott:* Would this also apply to radiation doses accumulated over a thirty year period?

*Dr Crow.* Yes Furthermore, you would expect about the same number in each of the following generations, the number gradually diminishing over a few dozen generations But, remember that gross abnormalities are probably a minor part of the total genetic effect I should think that heavy radiation of the ovaries is about as dubious as anything a radiologist is called on to do

*Dr. Scott.* In the December issue of the *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine* you will find the reports by Dr. Carl Braestrup and Dr G Failla where both approached this problem from different viewpoints and concluded that the shortening of the life span of radiologists was not an appreciable factor

*Dr. Tice:* I wonder how that figure of 15 days per roentgen ever got credence anyway?

*Dr Scott.* Well, I don't know Does anybody have that reference?

*Dr Brues.* Somebody took some figures for considerable amounts of life shortening and drew the usual straight line to the x, y axes This may or may not be legitimate. This is the figure you come out with if you make the assumption that each roentgen does an equivalent thing.

women for sterility. As I understand, he delivered a dose of about 75 r to the ovaries which is a big dose as compared with the doses we have been talking about today. His last report showed at least fourteen grandchildren from these women who had been irradiated. Of the 441 he followed, 270 became pregnant and had 247 children and 14 grandchildren. There were no abnormalities in any of these children. I would like to hear some discussion about these studies.

*Dr. Crow: With reference to Dr. Kaplan's studies, I was told* there were three with detectable abnormalities among the offspring. That's not large even for people who are not irradiated, since the total number involved was over 400, and the normal rate is about 1%.

*Dr. Tice:* When you take a chest film of a patient wearing a protective apron, do you think it lowers the gonadal dose?

*Dr. Paul Hodges:* We haven't been doing that. We have been limiting the size of our port very sharply to the size of the film. We are not using the apron

*Dr. Tice:* But the aprons are available?

*Dr. Paul Hodges:* Yes.

*Dr. Tice* They seem to create a mental hazard in the patient. We use similar size aprons for children We had a similar experience to yours A porter in a hospital had to have a chest film at yearly intervals or not get a salary check because it was required He refused without having a full length lead apron from his neck to his ankles Of course, he didn't realize how silly the request was because under this situation no radiation could reach the film. We finally convinced him that he didn't need the long apron.

*Dr Scott:* Would anybody like to talk about Shields Warren's report for Dr. Tice? Dr Crow?

*Dr. Crow:* I don't think I can say anymore than I said earlier. The difficulty is in the lack of the proper age corrections. In fact, Dr. Warren's was not the first study of this kind The first was done by a group from the Metropolitan Life Insurance Company. They did include the age correction They found, if I remember correctly, that radiologists differed from the

means that we get a fair number of 11 and 12-year-olds but the 3, 4, and 5 year-olds that used to give us so much trouble do not come to us

*Dr Scott:* That would apply also to the surveys made by the mobile tuberculosis units. In the statement from the national office they recommend that the mobile units be used only in areas and among groups in which they expect a high yield. They no longer recommend its use for grade school and high school groups and prefer to have them subjected to tuberculin tests

*Dr. Friedell:* I want to hark back to the fact that one had better know whether there is a threshold or not. This, in my opinion, is a function of understanding the mechanism and the dose response curve The decisions that one will have to make are going to depend on how one interprets the dose response curve, because this tells you whether there is a threshold and whether the effects are cumulative

I would like to reiterate that the data for mutations look better than the data for somatic effects, but are not conclusive. If a threshold does exist, it ameliorates the whole problem of radiation protection considerably. I suppose from the point of view of how one proceeds, it is probably most cautious and most judicious to assume that perhaps none exists. But if this in any way seriously embarrasses the use of x-ray for the diagnosis and treatment of disease, more careful scrutiny of the whole problem will be necessary

*Dr Scott* Dr Francis, we have not heard from you

*Dr Herbert Francis:* I think one of the big problems we have at our hospital is at the "polio" center I am distressed over the large amount of x-ray diagnostic work that is necessary on these patients They have bone malformations and deformities which require a lot of orthopedic work. They have urinary calculi commonly, lung and chest conditions, and frequently have collapses of vertebrae I have tried for a long time to figure out how best we can protect them during pyelograms For adults we have used two or three exposures over the kidneys with protection of the lower part of the tract by lead shields. For the chest films of course, there is always protection below their belt

*Dr. Scott:* Furthermore, wasn't that extrapolated from studies on mice?

*Dr. Brues:* This was extrapolated largely from mice, with a factor — one obviously has to put a factor in — encompassing the different life spans of the species. Could I comment on one other thing? In case there has been a misunderstanding. There is no question but that radiologists have shown a very much higher incidence of leukemia. We've been talking about life span — that's another thing.

*Dr. Scott:* You're satisfied that the statement that radiologists do have a higher incidence of leukemia is a solid observation?

*Dr. Brues:* This is a solid observation, yes This represents between a six and tenfold increase over the general leukemia rate The current guess as to the dose received by the average radiologist during his years of work is about 2,000 roentgens This would not be uniform total body radiation — although their exposure is considerably more diffuse than that of the patients. Incidentally, a little calculation will show that this in itself, would throw doubt on the figures that have been put out regarding life shortening per roentgen in man.

*Dr. Peterson:* Do you feel we should eliminate all unnecessary examinations and does this apply to the photofluorograms of the chest?

*Dr Hodges:* I certainly don't think that chest microfilms are unnecessary except in the case of children but for several reasons it is unwise to microfilm children On one hand, they are amenable to skin testing as a preliminary screen and, on the other hand, they are poor subjects Frequently they are unwilling or unable to cooperate and hold up the line by crying, sitting down on the floor, twisting and failing to hold their breath as the exposure is being made. Even under the best of conditions it is difficult to avoid administering unnecessary radiation, sometimes directly to the gonads We have stopped examining children and have the cooperation of our pediatricians in the decision Only when the examining physician believes that a child has about the build of a small adult is he sent for microfilming This

means that we get a fair number of 11 and 12-year-olds but the 3, 4, and 5-year-olds that used to give us so much trouble do not come to us

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Many of these are very small children. The doctors in attendance feel these are important examinations and they need them. We have changed some of the time intervals where they did routine examinations every month or so to see the progress of this or that — changed those to every two, three, or four months and with more clear cut indications for them. Overall I'm sure that these children are getting a considerable amount of radiation. It will be an interesting group in the long run to study. I think this would be true in all polio centers.

*Dr. Wilson:* No comments, except to express appreciation to these geneticists who have come here to give us a background in genetics in which some of us are seriously lacking. I am very grateful for the opportunity of listening to them.

*Dr. Scott:* We certainly are grateful to the geneticists and radiobiologists for coming here and giving us so much of their time I second everything Dr. Wilson said.

*Dr. Sante.* Could I speak just a moment about something that has always concerned me from the time I heard of it many years ago? With all this talent here maybe we can have some suggestions. Many years ago, it was reported from the Crocker Institute by its representative, Francis Carter Wood, I think, of a very interesting reaction of laboratory tumors to the effects of radiation.

Laboratory animals injected with a laboratory tumor (Jansen Rat Sarcoma) could be successfully transplanted in 100% of the inoculations After growth was well established, subjection to an adequate known dosage of x-radiation would cause complete regression. Now, if a cancerocidal dose of x-radiation were given to well-established tumor transplants and one-half of them were excised after three or four days, emulsified and re-injected into another group of rats, there would be about 87% takes. And consistently the tumor halves which were left in vivo and in situ went on to spontaneous destruction This has always been a very intriguing thing to me and I can't quite figure it out Are there any thoughts?

*Dr. Scott:* Do we have any help for Dr Sante?

*Dr. Brues.* I believe that experiment has been verified in

one or two other laboratories since then. In other words, I think it is correct to say that the state of vascularization at least around a transplanted tumor is an important factor.

*Dr. Sante:* Always favorable? Or is it sometimes unfavorable to have vascularity? What are the factors?

*Dr Brues:* At least in the case of a transplanted tumor it seems to be. Anyway, that's the way it comes out.

*Dr Tice* I would just like to comment on the pseudoscientists I had an experience just a couple of months ago. I received a telephone call from a doctor in northern Kansas. The patient was being treated by another radiologist The patient was very disturbed because the radiologist had indicated he was going to give her 2400 roentgens She told a physicist who was a relative about this and the physicist said that was terrible, that 400 r was the dose total a person should have and such a dose would be entirely impossible to give and shouldn't be given This physicist is one example of the type of people who are passing out misinformation

*Dr Scott* There is no doubt about that, and the purpose of this Conference is to disseminate accurate information to avoid such misconceptions

*Dr Crow* There is some hope to learn more about the genetic problem, although all of our discussions thus far may have sounded pretty futile from the standpoint of human beings If you expect it to be learned from direct study of human pedigree that pessimism is pretty much justified I wanted to point out in answer to points you made this morning, that tissue culture does offer some hope, at least We can study mutation of somatic cells to blood grouping to compatability antigens or to characteristics which influence growth of tissue colony If one were able to measure a variety of human tissues to a variety of mouse tissue if those would turn out to be comparable, that would give me a bit more faith in our present estimates based on the mouse On the other hand, if it turned out to be totally incomparable, then I think we are pretty much lost in any immediate effect

*Dr Paul* The question of what constitutes a necessary x-ray

Many of these are very small children. The doctors in attendance feel these are important examinations and they need them. We have changed some of the time intervals where they did routine examinations every month or so to see the progress of this or that — changed those to every two, three, or four months and with more clear cut indications for them. Overall I'm sure that these children are getting a considerable amount of radiation It will be an interesting group in the long run to study. I think this would be true in all polio centers.

*Dr. Wilson:* No comments, except to express appreciation to these geneticists who have come here to give us a background in genetics in which some of us are seriously lacking. I am very grateful for the opportunity of listening to them.

*Dr. Scott:* We certainly are grateful to the geneticists and radiobiologists for coming here and giving us so much of their time I second everything Dr. Wilson said

*Dr. Sante:* Could I speak just a moment about something that has always concerned me from the time I heard of it many years ago? With all this talent here maybe we can have some suggestions. Many years ago, it was reported from the Crocker Institute by its representative, Francis Carter Wood, I think, of a very interesting reaction of laboratory tumors to the effects of radiation.

Laboratory animals injected with a laboratory tumor (Jansen Rat Sarcoma) could be successfully transplanted in 100% of the inoculations. After growth was well established, subjection to an adequate known dosage of x-radiation would cause complete regression. Now, if a cancerocidal dose of x-radiation were given to well-established tumor transplants and one-half of them were excised after three or four days, emulsified and re-injected into another group of rats, there would be about 87% takes. And consistently the tumor halves which were left in vivo and in situ went on to spontaneous destruction This has always been a very intriguing thing to me and I can't quite figure it out Are there any thoughts?

*Dr. Scott:* Do we have any help for Dr Sante?

*Dr. Brues:* I believe that experiment has been verified in

all the time. Dr. Hodges touched on that business of exclusion, but I believe that we have to be not only considerate, but at the same time adamant as regards the use of x-rays As has been stated before, we have to inform them a little more strongly than we have in the past. We are attempting to do that, and that is why I use the term, "a voice in the wilderness." It is a difficult job, but it can be done, particularly when you insist that the clinicians consult with you in requesting that this or that be done on a requisition. We have got to go out and do a little bit more consulting, even if it means leaving our seat in the viewing room or fluoroscopic room, and going to the wards and talking to them This is what we have to do, and I think it is going to pay off, but it is going to take time.

*Dr. Scott.* That is the trend in radiology The day of the "film readers" is gone.

Dr Evans, we are indebted to you for serving as Co-Chairman of the Conference and in helping me build this program. Would you like to close the discussion?

*Dr. Evans* I would just like to say that from the standpoint of the biologists and geneticists that we don't mind associating with you radiologists at all We would like to have the opportunity again some time, and as Dr Brues indicated, biologists can learn a lot about tumors and abnormal conditions, etc, but we cannot attempt to work with physicians about radiation. I think we are going to turn more and more to the radiologists and we are going to expect the radiologists to pass the information on to other physicians Maybe we are adding a little more burden to them, but now I believe even the diagnostic radiologist is going to have to learn something about biological effects of radiation and the genetic hazards so that he can talk about them to other physicians as well as to students When you go back we would like you to realize that you have represented the other radiologists in your departments So pass the word along and get them in discussions Any one of us would be glad to carry on the discussion by correspondence For example, as Dr. Sante mentioned, I think I can give you some references on recent papers on tumor bed, radiation, etc We certainly have learned a lot and have enjoyed

examination I think is a very difficult one to make. Certainly in the conduct of progress examinations, one can space them at proper intervals and one can suggest to the patient's physicians the best interval. I have had the experience and am sure you have had the same sort of experience in examining a patient. This happened to be a woman in her early forties whose mother had died of a carcinoma of the stomach about six weeks previously. She came in and stated she had the same symptoms as her mother. *She felt she too was getting carcinoma of the stomach.* Her physician didn't think so, but had her gastro-intestinal tract examined and she had a carcinoma of the stomach It shook him very badly. That is not an isolated observation I think that one has to be very cautious about deciding that any given patient shouldn't have an x-ray examination merely because the symptoms are not definite.

*Dr. Scott:* I agree with you. I believe the decision for an examination remains the responsibility of the attending physician That is his right and his duty We can help most by supplying him with the necessary information and background so that he can exercise proper judgment.

*Dr. Lodwick* To me this has been a very informative and useful conference and I appreciate very much the opportunity to be here.

*Dr Van Epps.* I think that radiologists, although they may be thought of as voices crying in the wilderness at present, must go back to the fundamental concept that they are first of all physicians I feel that I have just as much information and knowledge in regard to medicine as other physicians I realize, Dr. Paul, the problem that some physicians may present I feel very strongly that it should be up to us to not only get the students, as Dr. Pirkey mentioned, but also the residents and the staff of all our departments to go back to the old philosophy of clinical medicine. I don't think the philosophy of clinical medicine today pervades in many departments It's a matter, in my opinion, of being an interpreter of returned requisitions and consultations Clinicians haven't gone back to the matter of trying to *confirm* a diagnosis. They go to the point of trying to *exclude* something

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it, and I think I speak for the others.

*Dr. Scott:* Thank you, Dr. Evans. We agree with you. Radiology has never had a basic science group as a foundation. It is by our close association with the radiobiologists, the radiochemists, the radiophysicists and the geneticists that radiology can *have a basic science group to back it up and from which we can* make progress. By working together, we can go further and faster. The Conference is adjourned.